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Male Breast Cancer: A Comparative Analysis from the National Cancer Database

Elizabeth B. Elimimian[1], Leah Elson[1], Hong Li[2], Hong Liang[1], Nadeem Bilani[1], Emily C. Zabor[2,3], Abby Statler[3], Zeina Nahleh[1]

[1]*Department of Hematology-Oncology, Maroone Cancer Center, Cleveland Clinic Florida, Weston, FL,* [2]*Department of Quantitative Health Sciences, Cleveland Clinic,* [3]*Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA*

Purpose: Breast cancer (BC) in males accounts for <0.5% of all male cancer diagnoses and ~1% of all BCs in the United States. We sought to describe clinicopathologic characteristics among male and female BC patients and differences in overall survival (OS) through the National Cancer Database over 13 years (2004–2016).

Materials and Methods: Secondary to the 1:99 ratio of male to female BC cases, we randomly selected female cases for equal comparison to males cases by diagnosis year. Chi-square and t-tests compared demographic and tumor characteristics. OS was examined using Kaplan–Meier survival analysis.

Results: Among the ~2.7 million BC patients, 9 per 1,000 BCs were in males, the rate remained similar over time. The mean (SD) age was 64.9±13.0 years for males and 60.7±13.6 years for females. Most of the male BC cases were white (non-Hispanic) (n=19,015 [80.2%]), clinical stage I (n=7,353 [32.1%]) or stage II disease (n=7,923 [34.6%]), and tumors were moderate or poorly differentiated (84.5%). Males exhibited more comorbidities, presented with a larger proportion of disease, and decreased OS (p<0.005) than females. Male OS was >10% lower at 5-years and nearly 20% lower at 10-years for males. More males had primary BC tumors under the nipple; the 10-year OS rate for this site was 48.8%.

Conclusions: This study reports clinicopathologic characteristics of a large cohort of male BC. Males present at older age, with a greater comorbidity index, at later stages of disease. Increased education regarding the continued risks of male breast cancer may be warranted.

Keywords: Breast neoplasms, male; Epidemiology; Neoplasms; Patient-relative outcomes

INTRODUCTION

Currently, breast cancer in men accounts for <0.5% of all male cancer diagnoses made annually, and constitutes approximately 1% of all breast cancer cases in the United States [1]. Although male breast cancer is uncommon, its incidence is increasing [2,3]. Due to its rarity, men with breast cancer have been largely underrepresented in clinical trials and population studies. At present time, no results from prospective national or international clinical trials, solely focusing on male breast cancer patients, have been reported. This pau-

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Correspondence to: Elizabeth B. Elimimian https://orcid.org/0000-0001-5168-5781
Department of Hematology-Oncology, Maroone Cancer Center, Cleveland Clinic Florida, 2950 Cleveland Clinic Blvd, Weston, FL 33331, USA.
Tel: +1-954-659-5840, **Fax:** +1-954-659-5810, **E-mail:** dr.elizabeth.elimimian@gmail.com
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city of male-specific information necessitates the use of results from clinical trials focused on 'female' breast cancer patients to inform disease management. As such, the treatment of male breast cancer patients predominantly mirrors that of postmenopausal women [4].

While breast cancer represents a relatively small proportion of all diagnosed cancers among men, it is associated with one of the highest mortality rates. In 2019, the American Cancer Society reported that more than three times as many men will be diagnosed with testicular cancer than with breast cancer. However, paradoxically, over the last five years, more men have died from breast cancer than testicular cancer [5,6]. These reported findings underscore the importance of continuing research for male-specific breast cancer. Therefore, population-based studies may be helpful in providing significant insight into these rare tumor types, and may assist in the subsequent development of treatment guidelines and recommendations.

Using a large dataset extracted from the National Cancer Database (NCDB), we sought to investigate the demographic and clinical differences between male *vs.* female breast cancer patients, and how these differences may contribute to disparities in overall survival (OS). We also sought to further explore the mortality gap between male and female patients with breast cancer.

MATERIALS AND METHODS

1. Subject and ethics statement

After obtaining Cleveland Clinic Institutional Review Board (IRB) approval (No. FLA 19-044), we conducted a retrospective analysis of male and female patients diagnosed with breast cancer between 2004 and 2016, as reported to the NCDB. Male and female designations were made based upon biological sex. The NCDB is a United States cancer registry that serves as a repository for cancer diagnoses and clinical outcomes. Information in the NCDB represents more than 1,500 medical facilities utilizing standardized reporting measures approved by the Commission on Cancer and the American College of Surgeons [7]. Currently, the NCDB captures more than 70% of cancer cases diagnosed in the United States [7]. Access to the NCDB registry was achieved based on a Participant User File award granted to the principal investigator (Z.N.).

Using the NCDB dataset, we identified both female and male breast cancer patients with TNM Stage 0 through stage IV breast cancer, diagnosed between 2004 and 2016. The International Classification of Disease for Oncology (ICD-O3) codes were used to classify histologic information. The base population included n=2,696,734 primary cases of male and female breast cancer patients. Overall, 23,990 male patients were included in our analyses. Because of an approximate 1:99 ratio of male to female patients included within the dataset, the same number of female breast cancer patients as male breast cancer patients, in each diagnosis year, were randomly selected for this study using simple random sample method.

2. Statistical considerations

Chi-square and t-tests, where appropriate, were used to compare demographic and clinical characteristics between the male and sampled female group, including: categorical age (<50 years, 50–69 years, ≥70 years), race (white, black, Hispanic, Asian, and other including Pacific Islander, Native American, and other races), insurance type (not insured, private insurance, Medicaid, Medicare, other government), categorical income (<$30,000, $30,000–34,999, $35,000–45,999, ≥$46,000), area of residence (metro, urban, rural), clinical staging (0, I, II, III, IV), disease grade (well differentiated, moderately differentiated, poorly/undifferentiated), location of tumor at breast ("primary tumor site": axillary tail, upper-outer quadrant, upper-inner quadrant, central/nipple, lower-outer quadrant, lower-inner quadrant, overlapping), invasive behavior (yes or no), estrogen receptor (ER+) status (yes or no), progesterone receptor (PR+) status (yes or no), human epidermal growth factor receptor 2 (HER2+) status (yes or no), and Charlson–Deyo comorbidity score (0, 1, 2, ≥3). All variables included less than 10% of missing data, except for grade (11.7%) and HER2 status (52.2% overall; ~3% after 2010). HER2 status was not widely reported to the NCDB until after 2009. Follow-up time was calculated from the date of diagnosis to the date of death or last alive contact, and patients still alive were censored for OS. The Kaplan–Meier method estimated OS according to sex, and the log-rank test was used to compare sexes. Both 5-year and 10-year survival estimates are presented.

Multivariable analyses using Cox proportional hazard models were conducted to understand which demographic and clinical factors were independently associated with survivorship, in both male and female

The World Journal of MEN's HEALTH

Table 1. Baseline characteristics of study population

Variable	Total No. of subject	Male (n=23,990)	Female (n=23,990)	p-value
Age at diagnosis (y)	47,980	64.9±13.0	60.7±13.6	<0.001
<50		3,150 (13.1)	5,410 (22.6)	
50–70		12,378 (51.6)	12,574 (52.4)	
≥70		8,462 (35.3)	6,006 (25.0)	
Race	47,465			<0.001
White		19,015 (80.2)	18,686 (78.7)	
Black		3,123 (13.2)	2,861 (12.0)	
Hispanic		881 (3.7)	1,274 (5.4)	
Asian		499 (2.1)	746 (3.1)	
Other		194 (0.8)	186 (0.78)	
Insurance	47,096			<0.001
Not insured		566 (2.4)	466 (2.0)	
Private insurance/managed care		10,244 (43.6)	12,719 (53.9)	
Medicaid		1,032 (4.4)	1,408 (6.0)	
Medicare		11,301 (48.1)	8,744 (37.1)	
Other government		357 (1.5)	259 (1.1)	
Income	46,514			<0.001
<$30,000		2,742 (11.8)	2,432 (10.4)	
$30,000–34,999		3,671 (15.8)	3,501 (15.0)	
$35,000–45,999		6,197 (26.7)	6,272 (26.9)	
≥$46,000		10,630 (45.7)	11,069 (47.6)	
Area of residence	47,980			0.008
Metro		19,982 (83.3)	20,232 (84.3)	
Urban		2,975 (12.4)	2,793 (11.6)	
Rural		1,033 (4.3)	965 (4.0)	
Clinical staging	46,107			<0.001
Stage 0		2,914 (12.7)	4,697 (20.3)	
Stage I		7,353 (32.1)	9,674 (41.7)	
Stage II		7,923 (34.6)	5,837 (25.2)	
Stage III		3,267 (14.3)	2,049 (8.8)	
Stage IV		1,461 (6.4)	932 (4.0)	
Grade	42,364			<0.001
Well differentiated		3,307 (15.5)	4,514 (21.5)	
Moderately differentiated		10,658 (50.0)	9,238 (43.9)	
Poorly or undifferentiated		7,360 (34.5)	7,287 (34.6)	
Ductal histology	47,980	17,971 (74.9)	16,035 (66.8)	<0.001
Primary tumor site	47,980			<0.001
Axillary tail		57 (0.24)	103 (0.43)	
Upper-outer quadrant		4,082 (17.0)	7,941 (33.1)	
Upper-inner quadrant		1,238 (5.2)	2,581 (10.8)	
Central/nipple		7,879 (32.8)	1,385 (5.8)	
Lower-outer quadrant		974 (4.1)	1,674 (7.0)	
Lower-inner quadrant		643 (2.7)	1,327 (5.5)	
Overlapping/NOS		9,117 (38.0)	8,979 (37.4)	
Invasive behavior	47,980	21,008 (87.6)	19,264 (80.3)	<0.001
ER+	44,398	20,432 (92.1)	18,025 (81.2)	<0.001
PR+	43,888	18,261 (83.1)	15,520 (70.8)	<0.001
HER2+ (available 2010 or later)	22,928	1,481 (12.4)	1,564 (14.2)	<0.001

Table 1. Continued.

Variable	Total No. of subject	Male (n=23,990)	Female (n=23,990)	p-value
Charlson–Deyo score	47,980			<0.001
0		18,888 (78.7)	20,387 (85.0)	
1		3,741(15.6)	2,842 (11.8)	
2		976 (4.1)	562 (2.3)	
≥3		385 (1.6)	199 (0.83)	

Values are presented as number only, mean±standard deviation, or number (%).
NOS: not otherwise specified, ER+: estrogen receptor, PR+: progesterone receptor, HER2+: human epidermal growth factor receptor 2.

groups. Independent factors were identified from demographic and clinical factors listed in Table 1 (except for HER2 receptor status) using stepwise model selection procedures with significance level of p<0.01 as entry-criteria and p<0.001 as stay-criteria, due to the large sample size. For the first model, the hazard ratio (HR) for male compared to female was initially estimated using the inclusion of age, clinical staging, and Charlson–Deyo comorbidity score. For the next subsequent model, independent predictors were included with demonstrated impact on OS.

Due to biological differences, a gender stratified analysis was performed to identify common and uncommon predictors in both the male and female groups.

All statistical analyses were conducted with SAS ver. 9.4 (SAS Institute Inc. Cary, NC, USA). Two-sided p-values are presented, p<0.001 is considered as significant.

RESULTS

A total study population of 47,980 (23,990 males and 23,990 females) was included in our analyses. Male and female median (interquartile range) follow-up time from diagnosis to death or last contact was 4.0 years (1.9–6.9) and 4.7 years (2.3–7.7), respectively. Comparative demographic and clinical characteristics between groups are presented in Table 1.

Univariate analyses (Table 1) showed that the following demographic and clinical characteristics were significantly different (p<0.001) according to sex: age, race, insurance status, income, clinical staging, Charlson–Deyo comorbidity score, disease grade, primary tumor site, invasive behavior, ER+ status, and PR+ status. Of note at diagnosis, male patients were older, present with later clinical staging, exhibit worse disease grade, had more ductal histology, and worse comorbidity

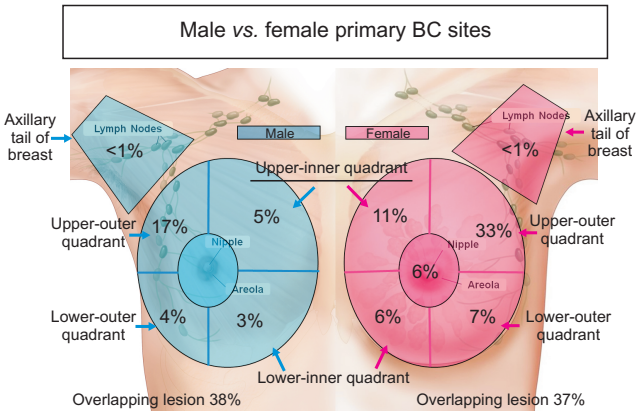

Fig. 1. Primary breast cancer (BC) tumor site, stratified by sex.

scores. In addition, the distribution of primary tumor site was different between male and females groups: with males exhibiting more central/nipple disease tendency (32.8% *vs.* 5.8%), and females exhibiting more upper-outer quadrant disease tendency (33.1% *vs.* 17.0%). There were similar rates of primary tumors with overlapping sites (Fig. 1). The male group also demonstrated a lower rate of private insurance coverage compared with the female group. Male breast cancer patients presented more frequently with ER+ (92.1% *vs.* 81.2%, p<0.001) and PR+ (83.1% *vs.* 70.8%, p<0.001) disease than female patients (Table 1).

Notably, males exhibited significantly worse OS (p<0.001) than females. The 5-year OS was 72.8% in males *vs.* 83.4% in females, and the 10-year survival was 52.5% in males *vs.* 69.1% in females (Fig. 2A). Additionally, the median OS was 10.7 years for the male group, but the median survival for the female group was not reached. The unadjusted hazard of early death was 75% higher (unadjusted HR, 1.75; 95% confidence interval [CI], 1.69–1.82) in males than in females (Fig. 2B). In a stepwise, multivariable model, after adjusting for age, clinical stage, and Charlson–Deyo comorbid-

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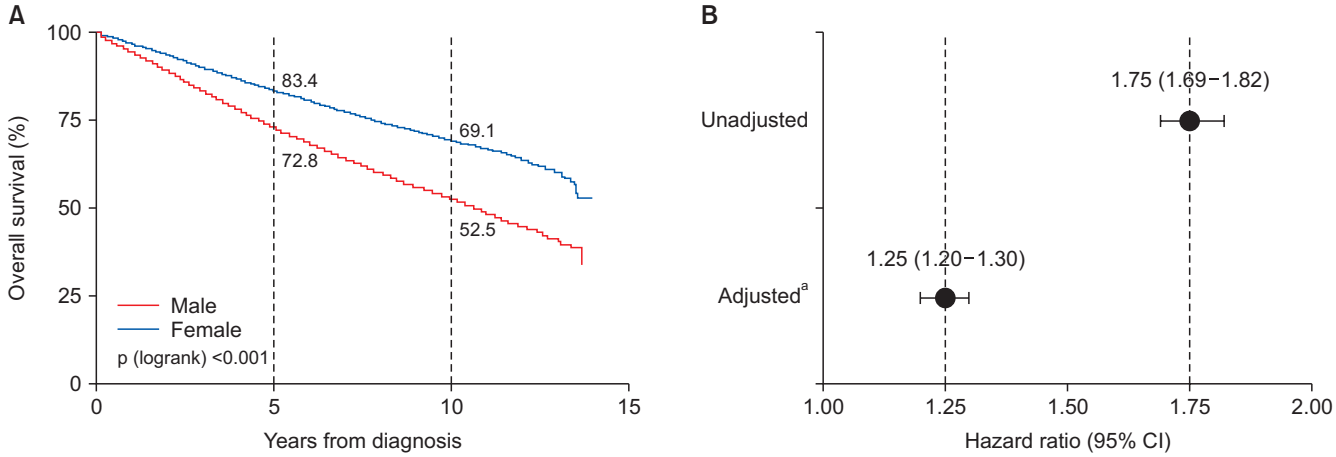

Fig. 2. (A) Comparison of overall survival (OS) in male and female breast cancer; numbers indicate % OS at 5-years and 10-years in each group. (B) Hazard ratio of death for male *vs.* female patients (adjusted and unadjusted). [a]Adjusted for age, clinical stage, and Charlson–Deyo comorbidity score. CI: confidence interval.

ity score, with 87.5% of the study sample, the hazard of early death was still observed to be higher in the male group (adjusted HR, 1.25; 95% CI, 1.20–1.30) (Fig. 2B). These results remained the same (adjusted HR, 1.28; 95% CI, 1.21–1.35) when expanding the analyses to a second, stepwise multivariable model to include additional independent protectors identified from this study and reported elsewhere, including: race, income, insurance type, grade, and both ER+ and PR+ status, in addition to the primary tumor site, which has been uniquely identified from this study with 70% of the study sample (Table 2). The age (mean, 62.9 *vs.* 62.2 years old), clinical staging (III or IV) (16.5% *vs.* 17.4%), and grade 3 (34.6% *vs.* 34.2%) were similar between patients included in multivariate analysis and those who were excluded. The 5-year (70.8% *vs.* 75.6%–84.9%) and the 10-year (48.8% *vs.* 58.4%–69.2%) OS for primary tumors originating under the nipple or the central breast location, was the worst compared to all other locations (Table 3).

Owing to the inherent biological differences between meles and females, multivariable analyses were next stratified by gender. All variables listed in Table 1 (except HER2+ status data, which was not available until after 2009) were included in the analyses to identify factors independently associated with OS separately for males and females (Table 2). Due to variance in completeness of data, the final multivariable model included 70% of the study population for both males and females after excluding cases with missing values. The top three factors identified as being associated with early death, in both males and females, were: late clinical stage, older age, and Charlson–Deyo score. Other factors associated with early death for both males and females included: being African American, having low income, using Medicaid insurance type, and presenting with poorer grade. With respect to uncommon factors, primary tumor site was associated with early death for males only (Table 2).

DISCUSSION

This analysis represents one of the largest studies evaluating demographic characteristics, clinical characteristics, and survival outcomes associated with gender disparities among patients with breast cancer. Similar to previous reports, patients with male breast cancer were more likely to have ER+ and PR+ tumors, ductal histology, and present at later stages of disease, compared to female patients with breast cancer [8-11]. Survival analyses in this study indicated that males with breast cancer have an observed survival disadvantage when compared to their female counterparts, demonstrating significantly poorer 5-year and 10-year OS. These results may be partially explained by independent factor analyses indicating that males were found to be older at diagnosis (mean age 64.9 years for males *vs.* 60.7 years for females), present with later stages of disease, exhibit different primary tumor location, and experience different disease management, when compared with females.

These findings corroborate earlier studies, which also

Table 2. Factors independently associated with OS in male and female

Variable	Male				Female			
	No. of subject	KM OS (%)	Cox multivariable		No. of subject	KM OS (%)	Cox multivariable	
		5-year OS (95% CI)	HR (95% CI)	p-value		5-year OS (95% CI)	HR (95% CI)	p-value
Stage								
Stage 0	2,679	89.6 (88.3–91.0)	1		4,312	93.9 (93.0–94.7)	1	
Stage I	6,665	83.7 (82.7–84.7)	1.36 (1.15–1.60)	<0.001	8,744	89.1 (88.4–89.9)	1.57 (1.34–1.83)	<0.001
Stage II	7,205	73.2 (72.0–74.4)	2.06 (1.76–2.42)	<0.001	5,355	82.3 (81.1–83.4)	2.46 (2.11–2.86)	<0.001
Stage III	3,003	58.1 (56.1–60.2)	3.38 (2.88–3.98)	<0.001	1,891	67.1 (64.8–69.5)	4.85 (4.13–5.71)	<0.001
Stage IV	1,313	19.8 (17.3–22.3)	12.26 (10.33–14.55)	<0.001	819	23.5 (20.1–26.9)	17.38 (14.61–20.68)	<0.001
Age (y)								
<50	2,917	84.1 (82.5–85.6)	1		4,997	90.7 (89.8–91.7)	1	
50–70	11,257	80.4 (79.5–81.2)	1.20 (1.07–1.35)	0.002	11,432	88.1 (87.4–88.8)	1.40 (1.24–1.58)	<0.001
≥70	7,712	57.8 (56.5–59.1)	2.64 (2.32–3.01)	<0.001	5,471	67.3 (65.9–68.7)	3.65 (3.17–4.20)	<0.001
Charlson–Deyo score								
0	17,245	76.8 (76.0–77.5)	1		18,637	85.4 (84.8–85.9)	1	
1	3,444	63.6 (61.7–65.5)	1.49 (1.39–1.60)	<0.001	2,590	75.9 (74.0–77.8)	1.29 (1.17–1.42)	<0.001
2	884	46.6 (42.8–50.4)	2.34 (2.09–2.61)	<0.001	508	60.7 (55.9–65.6)	2.09 (1.78–2.46)	<0.001
≥3	313	32.0 (25.9–38.0)	2.71 (2.31–3.19)	<0.001	165	45.5 (36.9–54.1)	3.56 (2.80–4.52)	<0.001
Insurance type								
Not insured	531	67.7 (62.9–72.4)	1.55 (1.27–1.88)	<0.001	437	76.8 (72.3–81.3)	1.40 (1.06–1.83)	0.016
Private	9,399	84.2 (83.4–85.1)	1		11,684	90.6 (90.0–91.2)	1	
Medicaid	927	67.4 (63.7–71.0)	1.72 (1.48–1.99)	<0.001	1,266	80.4 (77.9–83.0)	1.68 (1.44–1.97)	<0.001
Medicare	10,256	63.3 (62.2–64.4)	1.53 (1.41–1.65)	<0.001	7,898	73.6 (72.5–74.7)	1.50 (1.35–1.66)	<0.001
Other government	312	67.7 (61.2–74.3)	1.45 (1.11–1.90)	0.007	239	90.5 (86.3–94.8)	1.12 (0.71–1.77)	0.62
Grade								
1	3,023	83.0 (81.5–84.6)	1		4,121	88.9 (87.8–90.0)	1	
2	9,633	75.3 (74.3–76.3)	1.13 (1.03–1.25)	0.011	8,339	84.9 (84.0–85.8)	1.1113 (1.0005–1.2345)	0.049
3	6,735	65.9 (64.6–67.2)	1.41 (1.27–1.55)	<0.001	6,661	78.6 (77.5–79.8)	1.32 (1.17–1.48)	<0.001
Race								
White	17,403	72.8 (72.0–73.5)	1		17,146	83.6 (83.0–84.3)	1	
Black	2,798	68.3 (66.3–70.4)	1.05 (0.96–1.15)	0.28	2,571	77.1 (75.2–78.9)	1.15 (1.03–1.28)	0.012
Hispanic	805	80.7 (77.4–84.0)	0.66 (0.55–0.80)	<0.001	1,133	88.1 (85.9–90.4)	0.70 (0.58–0.86)	<0.001
Asian	447	80.8 (76.3–85.2)	0.755 (0.576–0.988)	0.041	669	90.6 (87.9–93.3)	0.63 (0.47–0.84)	0.002
Other	170	79.5 (71.9–87.1)	0.81 (0.53–1.24)	0.34	164	88.8 (83.1–94.5)	0.72 (0.41–1.27)	0.26
Income								
<$30,000	2,510	66.7 (64.5–68.8)	1.29 (1.18–1.42)	<0.001	2,192	76.5 (74.4–78.5)	1.19 (1.05–1.33)	0.004
$30,000–$34,999	3314	67.3 (65.4–69.2)	1.28 (1.18–1.38)	<0.001	3,203	80.4 (78.8–82.0)	1.13 (1.02–1.26)	0.016
$35,000–$45,999	5,645	72.4 (71.1–73.8)	1.12 (1.04–1.20)	0.002	5,748	81.8 (80.7–83.0)	1.02 (0.94–1.12)	0.59
≥$46,000	9,733	76.3 (75.4–77.3)	1		10,095	86.4 (85.7–87.2)	1	
PR status								
Negative	3,424	66.4 (64.6–68.2)	1.27 (1.18–1.36)	<0.001	-	-	-	-
Positive	16,515	74.1 (73.3–74.9)	1		-	-	-	-
ER status								
Negative	-	-	-	-	3,826	76.2 (74.7–77.7)	1.39 (1.26–1.52)	<0.001
Positive	-	-	-	-	16,360	85.1 (84.4–85.7)	1	

report the median age for male breast cancer patients to be in the 60s [2,12-14]. Older patients exhibit a higher variability of health, and may be less resilient to the toxicity of systemic or radiotherapies. Additionally, age related-immune dysfunction/immunosenescence results in an abnormal prolongation of inflammatory reactions

Table 2. Continued

Variable	Male				Female			
	No. of subject	KM OS (%)	Cox multivariable		No. of subject	KM OS (%)	Cox multivariable	
		5-year OS (95% CI)	HR (95% CI)	p-value		5-year OS (95% CI)	HR (95% CI)	p-value
Primary BC site								
Axillary tail	52	75.9 (63.2–88.5)	0.65 (0.33–1.31)	0.23	-	-	-	-
Upper-outer quadrant	3,711	79.2 (77.7–80.8)	0.911 (0.833–0.998)	0.044	-	-	-	-
Upper-inner quadrant	1,112	82.4 (79.8–85.0)	0.80 (0.68–0.93)	0.004	-	-	-	-
Central/nipple	7,104	69.0 (67.8–70.3)	1		-	-	-	-
Lower-outer quadrant	879	83.2 (80.3–86.1)	0.77 (0.65–0.92)	0.003	-	-	-	-
Lower-inner quadrant	574	81.5 (77.8–85.2)	0.77 (0.63–0.94)	0.010	-	-	-	-
Overlapping/NOS	8,454	70.2 (69.1–71.4)	0.98 (0.92–1.05)	0.65	-	-	-	-

OS: overall survival, KM: Kaplan–Meier, CI: confidence interval, HR: hazard ratio, PR+: progesterone receptor, ER+: estrogen receptor, BC: breast cancer, NOS: not otherwise specified, -: not available.

Table 3. Overall survival and primary breast cancer site (p<0.001)

Primary site	% of 5-year survival (95% CI)	% of 10-year survival (95% CI)
Overall	78.1 (77.7–78.6)	60.9 (60.2–61.6)
Axillary tail	79.7 (72.7–86.6)	63.8 (52.9–74.8)
UO quadrant	83.2 (82.4–84.0)	68.9 (67.6–70.2)
UI quadrant	84.9 (83.5–86.3)	69.2 (66.6–71.8)
Central/nipple	70.8 (69.6–71.9)	48.8 (47.0–50.5)
LO quadrant	84.0 (82.2–85.7)	68.3 (65.2–71.3)
LI quadrant	84.2 (82.2–86.1)	67.1 (63.7–70.5)
Overlapping	75.6 (74.8–76.3)	58.4 (57.2–59.6)

CI: confidence interval, UO: upper-outer, UI: upper-inner, LO: lower-outer, LI: lower-inner.

which may actually promote the progression or development of cancer [15]. In elderly patients, the immune system produces myeloid cells from the bone marrow at an increased frequency and subsequently decreases B and T cell progenitors [15]. Exposure to chemotherapy can accelerate these processes, making older patients more vulnerable to infection and chemotherapy-induced side effects [16]. Clinical trials which evaluate male breast cancer patients, stratified by age, would further the understanding of chemotherapy-dependent effects in elderly patients, at the cellular level.

Another possible contributing factor to the mortality differences noted between sex is the differences in stage at diagnosis. Our analyses revealed that male patients were diagnosed with later stage breast cancer, compared to female patients, a trend widely supported in the literature [8-11]. However, mortality differences between genders have been observed, even in early stages of breast cancer [17]. This supports the notion that factors beyond age and staging may also contribute to the survival disparities noted here. In fact, in this study, after adjusting for age, clinical stage, and comorbidity index, the risk of death for breast cancer among male patients decreased by 50%, but male were 'still' observed to exhibit a significantly higher risk of death than female.

Sex-based survival differences may also be due to primary tumor site. Among the unique observations of our analyses, is the effect of primary tumor site on breast cancer mortality, stratified by gender. Male with breast cancer had more tumors diagnosed under the nipple/central breast area (33%) compared to female with breast cancer (6%). This clinicopathologic difference may contribute to the adverse prognoses observed in male, as the 5-year OS for centrally-located breast cancers was significantly worse than tumors in the upper outer quadrant of the breast (71% *vs.* 83%, respectively). Similarly, at 10 years, the OS for nipple/central tumors was significantly worse than the survival rate for tumors in the upper-outer quadrant (49% *vs.* 69%, respectively). Unlike clinical grade, lymph node involvement, and hormone receptors and HER2 status, primary breast tumor location is not widely regarded as a prognostic factor. However, several studies have reported 'some' association between breast tumor location and OS. An analysis of 305,443 female with breast cancer, as recorded in the SEER database between 1990 and 2009, found that mortality was increased for primary tumors in the left central portion of the breast as well as the left and right lower outer quadrants [18]. Similar studies found that breast tumors in the me-

dial breast adversely impacted OS [19]. Although these studies focused on a smaller population of patients and included only females, our analyses adds to the existing literature and further suggests an association between primary tumor site and mortality.

Another possible explanation for the survival disparity between male and female breast cancer patients is based on management. A recent NCDB analysis, between 2004 and 2014, revealed a shift in the management preferences among male breast cancer patients, with more men choosing to receive mastectomy *vs.* breast-conserving surgery (BCS) [20]. One possible explanation for this trend is that male patients wanted to avoid the radiotherapy that accompanies BCS [14,20,21]. But Yadav et al [14] reported a possible correlation between total mastectomy and decreased OS. Additionally, there was a significant survival benefit for male patients who received adjuvant radiotherapy with BCS, even among stage I male breast cancer cases [14], which may underscore the potential importance of radiotherapy for patients with male breast cancer. Future research evaluating gender survival differences by management can improve the mortality of male breast cancer patients.

In our analysis, we noted that the 5-year OS was lowest for the following combination of factors for male patients with breast cancer: >70 years of age, >2 comorbidities, median income <$30,000, and insurance with Medicare (compared to other types of insurance). Unfortunately, the clinical characteristics of those with the poorest survival outcomes among their respective subcategory is typically not reflective of the majority of patients recruited into clinical trials. For instance, older patients are significantly underrepresented in clinical cancer trials [22]; while younger, healthier, and more highly educated patients are well represented [23]. Even those over the age of 64 years, with universal access to Medicare, were found to be less likely to participate in a clinical trial [24]. This data calls for more inclusive participation in clinical trials as a crucial step towards addressing the survival gap between male and female breast cancer patients.

The current paucity of medical resources and male-specific preventative guidelines might also present an obstacle to closing the mortality gap between genders. Since the implementation of public health initiatives in the 1980s, which promoted the use of screening mammograms, breast cancer mortality rates among women have decreased significantly [25]. In fact, the female breast cancer death rate reached its peak in 1989, and has been steadily declining in the years since [5], attributable to early detection via regular screening, symptom awareness, and management. The development and wide implementation of breast cancer screening recommendations for high-risk male populations might similarly lead to improvements in early detection and survival. Currently, breast cancer screening recommendations for male exist for those with a genetic predisposition (including BRCA1 or BRCA2 gene mutations) and/or a strong family history (1st degree relative with confirmed mutation or breast cancer diagnosis at age 40 or younger) [26]. The current clinical efficacy of the implementation of these guidelines remains unclear. It is our hope that the information provided from our analysis of the NCDB is used to shape future medical guidelines and practical recommendations towards the management of male breast cancer.

The strengths of this analysis include: 1) the 13-year duration of data collection, which allowed for the calculation of median survivorship in males and for the analysis of patient outcomes over time; 2) the large sample size of males, considering the rarity of this disease; 3) utilizing data collected from a national registry which allowed for a homogenous sampling of patients across accredited centers in the United States; 4) the standardized method of data collection within the NCDB which maximized the fidelity of the data collected. The limitations of this study include those that are typically encountered when utilizing a registry-based data set such as limited pathologic information, comorbidity information limited to categorical ranking, and lack of detailed treatment categories.

CONCLUSIONS

This analysis of a large population of male and female patients, diagnosed with breast cancer between 2004 and 2016, suggests that male patients with breast cancer were older at diagnosis, exhibited more comorbidities, presented with a larger proportion of disease metastasis, and exhibited more poorly differentiated tumor grades. Independent factors found to be associated with poorer OS were: male sex, older age, African American ethnicity, presenting with 2 or more comorbidities, having lower income, presenting at later clinical staging, and having poor tumor differentiation.

Based on the above data, we propose four recommendations: 1) strongly implementing specific breast cancer screening recommendations for high risk male; 2) considering sex specific differences including primary tumor site as prognostic criteria with implications on mortality and treatment *e.g.*, inclusion of radiation; 3) widening the clinical trials eligibility criteria to include historically underrepresented male with breast cancer; and 4) increasing efforts to promote awareness of disparities in male *vs.* female breast cancer.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: EBE, ZN. Data curation: ECZ, HL, HL. Formal analysis: ECZ, HL, HL. Supervision: ZN. Writing – original draft: EBE. Writing – review & editing: LE, NB, AS, ZN.

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