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ORIGINAL ARTICLE – BREAST ONCOLOGY

Gender Differences in Breast Cancer: Analysis of 13,000 Breast Cancers in Men from the National Cancer Data Base

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ABSTRACT

Purpose. To examine gender-specific differences in breast cancer utilizing the National Cancer Data Base (NCDB).

Methods. Breast cancer patients entered in the NCDB from 1998 through 2007 were compared by gender for demographics, tumor characteristics, treatment, and outcomes.

Results. A total of 13,457 men were compared to 1,439,866 women. Men were older, more often African American, less often Hispanic, had larger tumors, less often had low-grade disease, less often had stage 0 or I disease, and were more likely to have metastases to lymph nodes and/or distantly. Cancers in men were less likely lobular and more likely estrogen receptor and/or progesterone receptor positive. Men were more likely to have total mastectomy and less likely to receive radiotherapy. There was no difference in chemotherapy and little difference in hormone therapy rates. Differences in overall survival (OS) were highly significant ($p < 0.0001$): 83 % 5-year OS for women with breast cancer (median survival 129 months) versus 74 % for men (median survival 101 months). Women had better 5-year OS ($p < 0.0001$) for stage 0 (94 vs. 90 %), stage I (90 vs. 87 %), and stage II (82 vs. 74 %) breast cancer. There were no differences in 5-year OS for stage III (56.9 vs. 56.5 %, $p = 0.99$) or stage IV (19 vs. 16 %, $p = 0.20$) disease.

Conclusions. At first glance, this large study demonstrated numerous gender-specific differences. However, after accounting for differences in presentation, absence of data on disease-specific survival, and inherent deficiencies in reporting cancer registry data, breast cancer in men and women appears more alike than different.

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Breast cancer in men is rare. In a recent large international population-based study, men represented 0.6 % of all breast cancer patients.[1] In that study, which compared 2,665 men to 459,846 women with breast cancer, the incidence rate, over a 40-year time period, remained the same in men, 0.4 per 100,000 person-years, while in women, the rate increased by more than 50 %, from 51.4 in the early 1970 s to 80.3 by 2010. It has been more than 10 years since the National Cancer Data Base (NCDB) was queried for a study of breast cancer in men.[2] In that study, Scott–Connor et al. matched each male patient with a female patient, treated at the same institution, for age (within 5 years), ethnicity, income category, and disease stage. Because of the matched-pairs methodology, information regarding gender-specific differences in demographics, tumor characteristics, and overall treatments and outcomes was lacking or incomplete. Our purpose was to utilize the NCDB to highlight gender-specific differences in as many aspects of breast cancer as are collected in the NCDB.

METHODS

Source of the Data and Patient Selection

The NCDB is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons (ACoS) and the American Cancer Society.[3–6] The NCDB, established in 1989, is a nationwide, facility-based,

comprehensive clinical surveillance resource oncology data set that captures 70 % of all newly diagnosed malignancies in the United States. These cases come from approximately 1,500 CoC accredited cancer programs. It is the world's largest oncology outcomes database and contains information about more than 26 million cancer cases. Access to this data was provided the authors as part of the NCDB's alpha test of the Participant Use File program.[7] Patients with breast cancer whose data were entered in the NCDB from 1998 through 2007 were the subject of this study (ICD-O-3 codes 8XXX—any breast carcinoma).[8] The patients were compared for differences in gender, and then for age, race/ethnicity, histology, grade, tumor size, lymph node involvement, and clinical and pathologic tumor, node, metastasis (TNM) stage, using the American Joint Committee on Cancer staging system in effect at the time of data entry, hormone receptor status (only available for patients entered from 2004 through 2007), course of first treatment, length of follow-up, and overall survival (OS).[9] Disease-specific survival is not recorded in the NCDB.

Statistical Analysis

Statistical significance was by chi-square test for categorical variables and by nonparametric test for continuous variables. Survival rates were calculated by the Kaplan–Meier method and compared by the log rank test, then evaluated by gender, and then by stage of disease. Statistical significance was set at $p \leq 0.05$. Analyses were conducted by JMP software, version 8.0.2 (SAS, Cary, NC).

Data Confidentiality

The ACoS has a business associate and data-use agreement with each of its CoC-accredited hospitals. Data reported to the NCDB are retrospective, and no patient or physician identifiers are collected. The NCDB alpha Participant Use File is a deidentified data file per the regulatory and privacy requirements of the Health Insurance Portability and Accountability Act of 1996.[10]

RESULTS

Results are tabulated in Tables 1, 2, 3, 4, 5. Kaplan–Meier survival curves, by disease stage, are provided in Fig. 1. Concerning statistically significant differences in studies of large databases, small differences, although statistically significant, may be of little clinical importance, as described in an update of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 clinical trial.[11]

DISCUSSION

Because breast cancer in men is rare, individual institution studies of the disease, even in the case of high-volume centers, have had fewer than 100 cases for study. A recent example is reported from the Moffitt Cancer Center, looking at their 20-year experience of over 19,000 patients treated for breast cancer.[12] Only 73 (0.4 %) were men, and of these, only 62 had sufficient data recorded for inclusion in the study. The largest population-based data repository in the United States is the surveillance, epidemiology, and end results (SEER) program, a registry program of the National Cancer Institute, but it collects data from only a limited sample of registries in just 12 states, mainly on the basis of "their ability to operate and maintain a high quality population-based cancer reporting system and for their epidemiologically significant population subgroups."[13] In 1999, Mettlin et al.[14] compared data for common cancers, including breast cancer, collected by the NCDB and SEER for a single year, 1992, and found that the data matched closely. The most notable difference was that SEER collected data on 18,322 breast cancer cases that year, while the NCDB collected data on 96,323 breast cancer cases—five times as many. The data collected by the NCDB represent more than 70 % of all cancer cases diagnosed and treated in the United States and is much more geographically diverse than the data collected by SEER.

Gender differences in race and ethnicity were small and likely not clinically important, but because of the large numbers involved, statistical significance was reached. Most breast cancer patients in our study were white—85.7 of men and 86.8 % of women. A total of 11.7 % of men with breast cancer were black, compared to 9.9 % of women; 3.6 % of men and 4.5 % of women were Hispanic. O'Malley et al., using SEER data, examined racial and ethnic differences in 1,979 men diagnosed with primary invasive breast carcinoma between 1973 and 1997.[15] In their study, 82 % of men with breast cancer were white and 11 % were black.

TABLE 1 Comparison of breast cancer in men and women by race and ethnicity

Race/ethnicity	Men (n = 13,457)	Women (n = 1,439,866)
White	11,340 (85.7 %)	1,232,298 (86.8 %)
Black	1,548 (11.7 %)	141,408 (9.9 %)
Asian, Pacific Islander	232 (1.75 %)	35,616 (2.51 %)
Native American	21 (0.16 %)	35,616 (2.51 %)
Other	91 (0.69 %)	8,129 (0.57 %)
Non-Hispanic	11,741 (96.4 %)	1,258,409 (95.5 %)
Hispanic	438 (3.6 %)	58,954 (4.5 %)

TABLE 2 Comparison of breast cancer in men and women by age and tumor characteristics

Characteristic	Men ($n = 13,457$)	Women ($n = 1,439,866$)	p[a]
Median age, years (range)	63 (19–20)	59 (19–90)	<0.00001
Median tumor size, mm (range)	20.0 (1–902)	15.0(1–988)	<0.00001
Lobular histology (%)	1,383 (10)	264,203 (18)	<0.0001
Histologic grade 1 (%)	1,829(16.0)	248,715 (20.7)	<0.0001
Metastasis to regional lymph nodes (%)	4,389 (41.9)	363,040 (33.2)	<0.0001
Distant metastasis (%)	495 (4)	38634 (3)	<0.0001
Estrogen receptor positive (%)	4,654 (88.3)	397,914 (78.2)	<0.0001
Progesterone receptor positive (%)	3,972 (76.8)	335,052 (67.0)	<0.0001

[a] All values are statistically significant (chi square test)

TABLE 3 Breast cancer in men and women according to clinical and pathologic stage grouping

Stage	Men	Women
Clinical	($n = 5,561$)	($n = 637,439$)
0	1,001 (18 %)	164,540 (26 %)
I	1,917(35 %)	244,011 (38 %)
II	1,576 (28 %)	141,766 (22 %)
III	558 (10 %)	47,726 (8 %)
IV	509 (9 %)	39,396 (6 %)
Pathological	($n = 10,927$)	($n = 1,170,930$)
0	1,136(10 %)	166,818 (14 %)
I	3,675 (34 %)	497,787 (43 %)
II	4,272 (39 %)	384,208 (33 %)
III	1,496(14 %)	99,965 (8 %)
IV	348 (3 %)	22,152 (2 %)

TABLE 5 Comparison of breast cancer in men and women by outcome

Stage	Gender	n	Median OS (mo)	5-year OS (%)	P
All stages	Male	5,901	101	74	<0.0001*
	Female	720,082	129	83	
Stage 0	Male	698	Not reached	90	<0.0001*
	Female	124,718	Not reached	94	
Stage I	Male	1,827	109	87	<0.0001*
	Female	280,751	130	90	
Stage II	Male	2,253	Not reached	74	<0.0001*
	Female	223,620	126	82	
Stage III	Male	606	72.1	56.5	0.99
	Female	46,912	72.7	56.9	
Stage IV	Male	310	18	16	0.20
	Female	24,463	20	19	

OS overall survival

*Statistically significant (log rank test)

The median age of men in our study with breast cancer was 63 years, 4 years older than women ($p < 0.00001$). In the largest SEER study of breast cancer in men, men with breast cancer were 67 years old, on average, compared with 62 for women.[16] In the international study of breast cancer in men versus women that we cited earlier, men were 70 years old, versus 62 for women, at the time of diagnosis.[1]

Men in our study presented with cancers that were one-third larger than women, 20.0 versus 15.0 mm mean size at presentation ($p < 0.00001$). Breast cancer in men was less likely to be grade 1, 16.0 versus 20.7 % ($p < 0.0001$), and more likely to have lymph node metastasis, 41.9 versus 33.2 % ($p < 0.0001$). Distant metastasis was uncommon at presentation in both genders but was more frequent in men, 4 % versus 3 % ($p < 0.0001$). Speculating on the reason that men in their study and other studies routinely presented with more advanced disease than women with breast cancer, Giordano et al.[16] credit increased awareness of breast cancer among women and their health care

TABLE 4 Treatment of breast cancer in men and women

Treatment modality	Men ($n = 13,457$)	Women ($n = 1,439,866$)	p
Total mastectomy	8,459 (67 %)	521,409 (38 %)	<0.00001*
Radiotherapy provided or recommended	4,795 (35.9 %)	718,240 (50.4 %)	<0.0001*
Chemotherapy provided or recommended	5,379 (40.1 %)	569,847 (39.8 %)	0.40
Hormone therapy provided or recommended	5,528 (41.2 %)	607,102 (42.4 %)	0.006

* Statistically significant (chi square test)

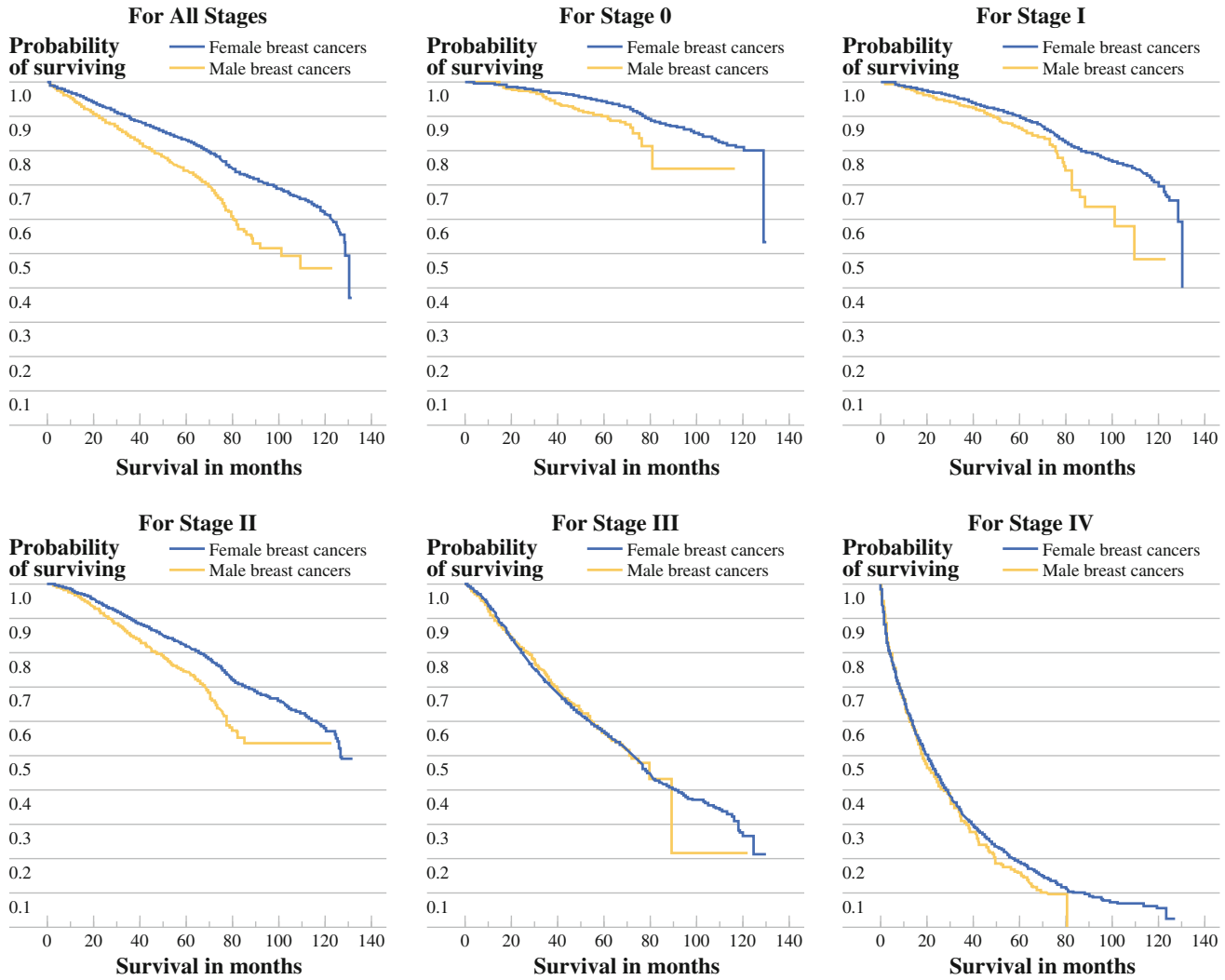

FIG. 1 Kaplan–Meier survival curves, by disease stage, for breast cancer in men and women

providers, as well as the existence of well-established guidelines for breast cancer screening for women. The differences in patient age and disease size and stage at presentation could represent lead-time bias in diagnosis. It could further be argued that by comparing tumor characteristics between men and women with breast cancer, such as size and stage, without separating out the women whose cancers were discovered through mammographic screening, is comparing apples to oranges, but unfortunately, cancer registry data sets do not allow us to make that distinction. In any event, increasing awareness of breast cancer in men and their health care providers could result in discovering the disease earlier and improving its outcome.

Lobular histology was much less common in the men with breast cancer whom we studied, 10 versus 18 % in women ($p < 0.0001$). This was also true in the Giordano study[16] that used SEER data, and in nearly every other study of breast cancer in men. In fact, 10 % is relatively high for the incidence of lobular cancer in men. The highest frequency that we could find in a previous report was 4.2 % from a Veterans Administration study by Nahleh et al.[17] We could not review the original pathology in the cases entered into our study for confirmation of histology. Many of these cases precede the now-common use of immunohistochemical testing with E-cadherin and similar agents to differentiate between true lobular histology and ductal histology with lobular features, as described by Acs et al.[18] It is likely that the frequency of lobular carcinoma in men (and women) in our study is overreported.

Men with breast cancer in our study were twice as likely (67 vs. 38 %, $p < 0.00001$) as women to undergo mastectomy. We would have expected the rate of total mastectomy to be even higher in men, approaching 100 %. This may represent underreporting, and/or it may reflect situations where an excisional biopsy was the only surgical

procedure. There is no way to tell without reviewing the original records, which is beyond the scope of this study. There were no differences in chemotherapy rates, 59.9 versus 60.2 %, $p = 0.40$), but considering that men presented with more advanced disease, this may represent underutilization of chemotherapy in men. In our study, we found that men were less likely to undergo radiotherapy, 35.9 versus 50.4 % ($p < 0.0001$), likely reflecting the higher partial mastectomy rate in women.

Despite an 88.3 % rate of estrogen receptor (ER)-positive breast cancers in men in our study, only 41.2 % of men with breast cancer received or were recommended to receive hormone therapy. Underreporting of hormone treatment data in the NCDB, SEER, and other cancer registry–based data sets, has been a problem, as these prescription-based therapies are often difficult to track (Andrew Stewart, senior manager, NCDB, personal communication). In 2004, the CoC introduced the Cancer Programs Practice Profile Reports (CP3R), in which hormone therapy for ER-positive breast cancer became a quality indicator, and this greatly improved reporting rates (and, perhaps, performance rates) for women with ER-positive breast cancer, from an average of 63 % in 2004 to 82 % in 2009.[19] A program of real-time reporting of quality indicator data in breast and colon cancer recently introduced by the CoC is expected to further enhance the quality and completeness of NCDB data, as well as improve the level of care at member institutions.[20]

In the Moffitt study, the authors used National Comprehensive Cancer Network guidelines to judge rates of compliance with recommended treatments. On the basis of these guidelines, chemotherapy, hormone therapy, and radiotherapy would have been indicated in 34 cases, 62 cases, and 14 cases of breast cancer in men, respectively.[12,21] Only 20 (59 %) of 34 received chemotherapy, 51 (82 %) of 62 received hormone therapy, and 10 (71 %) of 14 received postmastectomy radiotherapy.

Using duration of follow-up from date of diagnosis to last contact and status (alive or dead) at last follow-up, we calculated median OS, in months, and 5-year OS (Table 5). Median duration of survival was significantly shorter for men, 101 versus 129 months for women ($p < 0.0001$), and 5-year OS was significantly less for men, 74 versus 83 % for women ($p < 0.0001$). When 5-year OS was analyzed by stage, there was no difference for stage III disease (56.5 for men vs. 56.9 % for women, $p = 0.99$) or stage IV disease (16 for men vs. 19 % for women, $p = 0.20$). For each of the earlier stages, men had significantly worse 5-year OS. Stage 0 5-year OS was 90 for men and 94 % for women ($p < 0.0001$). Five-year OS for stage I disease was 87 for men versus 90 % for women ($p < 0.0001$). Five-year OS for stage II disease was 74 for men versus 82 % for women ($p < 0.0001$). The NCDB does not record cause of death or status of cancer at the time of last follow-up. Inability to calculate disease-specific survival or death due to cancer when comparing women with breast cancer, with men, who are, on average, older, and more likely to die sooner of unrelated causes, must be taken into consideration when considering these results. A generally reliable workaround for lack of disease-specific survival data is to calculate relative survival, the ratio of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer free individuals, adjusting for the general survival of the US population for that race, gender, age, and dates of observation.[22]

In the Giordano study[16], which used SEER data, median OS was 92 months, and the 5-year OS for men was 68 % for all stages, 78 % for stage I, 67 % for stage II, 40 % for stage III, and 19 % for stage IV disease. The overall 5-year survival rates were lower stage by stage for men versus women with breast carcinoma, with corresponding OS rates for women reported to be 88, 75, 49, and 16 %, respectively, for stage I–IV disease. However, the differences disappeared when relative survival rates were calculated. The relative 5-year survival rates for men with stage I–IV breast carcinoma were 96, 84, 52, and 24 %, respectively. For women, the corresponding rates were 99, 84, 55, and 18 %.

When NCDB data were used to compare men and women with breast cancer who were carefully matched for age, stage, treatment, tumor characteristics, and demographics, the survival outcomes were very different.[2] Relative survival curves were almost superimposable for the men and women in that study with stage 0, I, and II disease. The survival curves diverged somewhat for stages III and IV, with men showing worse 5-year survival rates than women, but this did not achieve statistical significance. At the least, one might say, from the study of Scott-Connor et al., that when matching men and women with breast cancer for age, tumor characteristics, treatment, and demographics, there is little difference in survival rates.[2]

In conclusion, we compared 13,457 breast cancers in men to 1,439,866 breast cancers in women recorded in the NCDB over a 10-year period and found marked differences in demographics, tumor biology and stage of disease at presentation, treatments offered, and OS. After accounting for differences in the ways in which breast cancers are detected in men and women, as well as the likelihood that these men, who are on average older than the women, had higher non-breast-cancer-related mortality, and after accounting for deficiencies in data collection and reporting by cancer registries, we conclude that breast cancer in men and women is more similar than different. We think that by increasing the awareness of breast cancer in men among men and their health care providers, and by adhering to the treatment guidelines already in place for the treatment of

breast cancer in women, the outcomes of breast cancer in men could be improved. This should be the focus of future studies.

CONFLICT OF INTEREST The authors have no conflicts or other disclosures.

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