Matched-Pair Long-Term Survival Analysis of Male and Female Patients with Breast Cancer: A Population-Based Study

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Abstract

Purpose: To examine the differences in long-term survival between male and matched female breast cancer cases based on data from the Shanghai Cancer Registry (SCR).

Methods: Every male breast cancer case was matched with four female cases according to the year of diagnosis, age, tumor stage, and histological subtype. Cumulative observed overall survival (OS) and cancer-specific survival (CSS) rates were calculated using Kaplan-Meier survival estimates, and log-rank tests were applied to compare the survival rates of male and female cases. Cox proportional-hazards regression models were used to assess the hazard ratios (HR) and 95% confidence intervals (CI) for the association between sex and the risk of death.

Results: 50,958 patients with breast cancer (0.85% male) were registered in the SCR between 2002 and 2013. After matching, 434 male and 1736 female patients were included in the study. With a median follow-up time of 10 years, men with breast cancer showed significantly worse OS ($P < 0.0001$) and CSS ($P < 0.0001$) than women. The 5- and 10-year OS rates for male and female patients were 67.27% and 77.75%, and 45.95% and 62.60%, respectively; the 5- and 10-year CSS rates for male and female patients were 70.19% and 79.79%, and 50.57% and 67.20%, respectively. Compared with women, men had 65% increased risk of overall death (95% CI: 1.42-1.92) and 70% increased risk of cancer-specific death (95% CI: 1.44-2.00).

Conclusion: The study provided evidence at the population level that male patients with breast cancer had lower survival rates than women in China.

Introduction

Compared with female breast cancer, male breast cancer incidence is very low, representing 0.6%-1.6% of all breast cancers among different populations [1-3]. On average, men tend to be diagnosed with breast cancer ten years later than women, reaching a peak at the age of > 65 years [2-4]. Moreover, they are often diagnosed at a higher stage than women, as the data from the Surveillance, Epidemiology, and End Results (SEER) program showed that the proportion of local-stage breast cancer in men was 20% lower compared to women [1], and several studies have described the biological differences between male and female breast cancer [5-7].

Previous studies indicated that male breast cancer patients' survival rates differed from female breast cancer patients; nonetheless, these results were contradictory [1]. Studies from North America or European countries reported similar or even better survival in male patients compared with female breast cancer [3, 8], while worse survival was observed among most studies in China [2, 9-12]. Moreover, because of the rarity of male breast cancer, most survival information on this disease has been obtained from small, single-institutional, or retrospective studies in China [9-13], with only one survival analysis being conducted at the population-based level with a small sample size of male breast cancer cases [2], which limited their interpretability. Additionally, given the distinct characteristics of male and female

breast cancer cases, such as age, TNM stage, and histological subtype, which are crucial for the prediction of survival, the matched-pair method could serve as an important study design to investigate the potential sex disparity in the survival of breast cancer.

Based on the Shanghai Cancer Registry (SCR), the oldest cancer registry in China and one of the largest single cancer registries in the world, we conducted the current sex-comparative study to explore the difference in survival between male breast cancer patients and matched female breast cancer patients, thus aiming to improve the understanding of the sex heterogeneity in the survival of patients with breast cancer in China.

Methods And Materials

Study population and data collection

Breast cancer cases in this study were derived from the SCR database, one of the largest cancer registries globally, and an associate member of the International Association of Cancer Registries (IARC). The complete cancer incidence and mortality data for urban and suburban areas have been collected since the year 2002, covering an average of 14 million permanent residents in Shanghai. The vital status of cancer cases was tracked via active and passive follow-up, the death information was obtained from the Vital Statistics Section of the Shanghai Municipal Center of Disease Control and Prevention by data linkage, and the survival and treatment information were collected by the community health service through home visits. Our previous study provided detailed information on the high quality of the cancer registry data in SCR [14]. Overall, the well-organized follow-up system resulted in a follow-up rate of more than 99% for Shanghai's cancer cases [15, 16].

Four hundred thirty-four men and 50,524 women were registered in the SCR as breast cancer cases between 2002 and 2013. The current study included all male cases registered with primary breast cancer diagnosed between 2002 and 2013 who were followed up until death or December 31, 2019. Every case was matched with four female cases from the original dataset. The matching process was based on four features relevant to breast cancer prognosis, i.e., age (within ±3 year), year of diagnosis (within ±4 years), tumor stage (I, II, III, IV, and unknown), as well as histological subtype [(Infiltrating ductal carcinoma (IDC), others, and unknown]. If more than four female patients were eligible, the best matches were chosen by random selection; if fewer than four female patients were available for matching, all of them were selected. The matching procedure was conducted in a blinded manner without any information about the patient’s outcomes.

Statistical Analysis

For male and all female breast cancer cases, the 5-year relative survival (RS) rates were calculated as the ratio of the net cancer-specific survival (CSS) rate to the expected rate, which was estimated from the general sex and calendar period-specific life tables for Shanghai residents using the Ederer II method [17]. For male and matched female breast cancer cases, cumulatively observed all-cause survival (OS) and

CSS rates were calculated using Kaplan-Meier survival estimates, and log-rank tests were applied to compare the survival rates of male and matched female cases. In addition, the 5-year OS and CSS rates were reported for these patients, while data of patients diagnosed during 2002-2009 who were followed for at least 10 years were used for calculating 10-year OS and CSS. Cox proportional-hazards regression models were used to assess the hazard ratios (HR) and 95% confidence intervals (CI) for the association between sex and the risk of overall and cancer-specific survival for male and matched female patients. Matching was accounted for in the Cox proportional hazards models by including a matching variable based on age, year of diagnosis, tumor stage, and histological subtype in the analysis. Analyses were conducted using SAS statistical software (version 9.4). All statistical tests were two-sided, and a *P*-value <0.05 was considered “statistically” significant.

Results

After excluding 18 (0.035%) cases without death date and 35 (0.069%) cases that were only recognized by death certification (DCO), 434 male and 50,471 female new breast cancer cases diagnosed from 1 January 2002 to 31 December 2013 among all population in Shanghai were included in the study. Based on the matching procedure and four matching criteria, 434 male cases were 1:4 matched with 1736 female cases were available for survival analyses. By December 31, 2019, 914 patients (231 men and 683 women) died, including 752 (196 men and 556 women) who died of cancer.

Table 1 shows the distribution of male, matched female, and all-female breast cancer cases according to the matching criteria and other characteristics. Compared with all female breast cancer cases in Shanghai, the male patients were nearly 10 years older at the time of diagnosis (mean age at diagnosis: 66.06 *vs*. 57.27, $P < 0.01$), they were more frequently diagnosed with higher TNM stage (stage III-IV: 71/238 *vs.* 7737/35,708) and more frequently with unknown TNM information (45.16% *vs.* 29.32%) ($P < 0.01$); the histology information was available for 73.5% of the male breast cancer cases, and the proportion of IDC was lower for male cases than female cases (54.38% *vs.* 70.70%) ($P < 0.01$); after matching, the difference disappeared.

The 5-year RS rates for male and all-female breast cancer patients diagnosed in Shanghai between 2002 and 2013 were 83.30% (83.22-83.37) and 86.55% (86.55-86.56), respectively (data not shown). After matching, men with breast cancer showed significantly worse OS ($P < 0.0001$) and CSS ($P < 0.0001$) than female patients, with a median follow-up time of 10 years (**Figure 1** and **Figure 2**).

The 5-year OS rates for male and matched female breast cancer patients were 67.27% (95% CI: 62.57-71.51) and 77.75% (95% CI: 75.70-79.66), respectively; and the 5-year CSS rates for male and matched female breast cancer patients were 70.19% (95% CI: 65.52-74.35) and 79.79% (95% CI: 77.79-81.64), respectively. Stratification analysis showed that men younger than 70 years old, with early TNM stage (stage I-II), and diagnosed as IDC subtype had better survival than men older than 70 years of age, with late TNM stage, and other histological subtypes (**Table 2**).

When restricted to cases diagnosed during 2002-2009, the median follow-up time was 13 years. The 10-year OS rate for male and female breast cancer patients was 45.95% (95% CI: 39.85-51.82) and 62.60% (95% CI: 59.62-65.42), respectively; and the 10-year CSS rates for male and matched female breast cancer patients were 50.57% (95% CI: 44.27-56.53) and 67.20% (95% CI: 64.26-69.96), respectively. The results of the stratification analysis are shown in **Table 3**.

Table 4 presents the results of a Cox proportional-hazards analysis for the association between sex and survival. Compared with women, the overall results showed that men had a 65% increased risk of overall death (95% CI: 1.42-1.92) and 70% increased risk of cancer-specific death (95% CI: 1.44-2.00). In the stratification analyses, the hazard of overall or cancer-specific death was greater for men younger than 70 years old (HR: 2.02 95% CI: 1.54-2.63; HR: 2.07, 95% CI: 1.57-2.74, respectively); men with early-stage (stage I-II) breast cancer (HR: 1.89, 95% CI: 1.40-2.56; HR: 2.00, 95% CI: 1.44-2.79, respectively); men diagnosed in early period (200-2005) (HR: 1.91, 95% CI: 1.52-2.40; HR: 2.04, 95% CI: 1.59-2.60, respectively); and men with histology subtypes other than IDC (HR: 2.64, 95% CI: 1.84-3.79; HR: 2.55, 95% CI: 1.71-3.80, respectively).

Discussion

To the best of our knowledge, this is the largest sex-specific survival study that considered the major established cancer and patient characteristics in breast cancer to elucidate potential sex-specific differences in the survival of breast cancer patients in China within a time span of more than 15 years. This study's main finding was the long-term survival of male patients with breast cancer that was significantly lower compared to female patients after matching for age, diagnosis year, TNM stage, and histological subtype.

Similar to previous reports, male patients in this study accounted for 0.85% of all patients with breast cancer and were more likely to receive a diagnosis at a later age and higher stage than female cases [1, 3, 18]. Men in this study were less likely to be diagnosed with a ductal histologic type (54.38%), which is not consistent with previous findings reported by studies in the SEER database and from European countries (>75%) [1, 19], A large number of missing histological cases in this study (26.50%), the population difference, and potentially different diagnostic criteria applied across different countries might partially contribute to this gap.

Our matched-pair study showed that the survival rate of male breast cancer was significantly lower compared to female breast cancer, which was in line with the observations reported in the single-institute studies from Guangdong, Tianjin, and Shandong, showing a worse prognosis for male breast cancer patients both in overall and disease-free survival [9-12]. Still, the population-based study from Hong Kong showed that male patients had poorer OS in an early stage but better breast-cancer-specific survival compared with their female counterparts [2], however, given the limited number of male cases (n=132) and breast cancer-specific deaths (n = 12), these results need to be further confirmed. The sample size is crucial in the analysis of population-based survival data. For instance, most US studies before the year

2015 showed similar overall survival rates for male and female breast cancer patients [8, 20-22]. Yet, the most recent updated analysis in the SEER program, which included 2254 men with early breast cancer, and in the National Cancer Database, which comprised 16,025 men with breast cancer, revealed a significant survival disadvantage for male patients [18, 23]. The results from a worldwide study including 2665 men diagnosed with breast cancer from 5 European countries and 1 country from southeast Asia were different from the findings of the present study, which revealed a better survival for male breast cancer patients than females after adjusting for region, time since diagnosis, age, and year of diagnosis, stage, and treatment (relative excess risk: 0.78, 95% CI: 0.62-0.97)[3], thus suggesting the regional diversity in the sex disparity of breast cancer survival.

Several possible factors might explain the sex disparity in the breast cancer survival rate. First, population-based studies have shown that the prevalence of breast cancer susceptibility gene 2 (BRCA2) mutations in men with breast cancer was 4%-16% [24, 25], which is slightly higher than that in women with breast cancer (around 4%) [26]. A meta-analysis showed that BRCA2 mutations are associated with worse overall survival among breast cancer patients [27]. Second, the treatment patterns for men differed from that for women, although male breast cancer patients' management was mainly extrapolated from the knowledge about female breast cancer [28, 29], compared with women, the compliance of adjuvant radiotherapy was lower for men among many countries [3], and more than 50% of men who were treated with breast-conserving surgery did not receive radiotherapy [4, 30], which could explain the more obvious sex disparity among patients with early-stage breast cancer in our study. In addition, our results confirming the changes in risk of death for male breast cancer patients that occur over time suggest that the improvement of treatment could narrow the survival gap between men and women but could not eliminate it. Third, the lifestyle risk factors, which are closely related to breast cancer survival, such as smoking and obesity, might be differently distributed among male and women breast cancer patients [31, 32].

This study has several limitations that need to be pointed out. The major limitation is the lack of information on the specific cause of death (breast cancer, other cancers, cardiovascular disease, and others) and factors closely related to breast cancer survival, such as treatment strategies [breast surgery, (neo)adjuvant chemotherapy, adjuvant radiotherapy, adjuvant endocrine therapy, etc.], molecular subtypes (estrogen receptor, progesterone receptor, androgen receptor, HER-2, etc.). The linkage of population-based cancer registry database and hospital-based treatment database is expected in the future to eliminate this limitation. Also, lifestyle factors (smoking, body mass index, etc.) were not available in this study due to the deficiencies of cancer registry data. Second, a large number of male breast cancer cases (45%) missed the information on the TNM stage, leading to the unprecise estimation of breast cancer survival. However, we matched male cases with female cases by TNM stage, including the missing class, which reduced the potential bias in the comparison of the sex disparity for breast cancer survival.

The study's strength includes the coverage of all residents in Shanghai, the well-established follow-up system of SCR, and the 17-year follow-up for overall and cancer-specific death, which enabled us to

examine the differences in long-term survival rates among men and women diagnosed with breast cancer in Shanghai, China. Additionally, the analysis was conducted using the matched-pair approach and considering the established factors that could affect breast cancer survival (age, diagnosis year, TNM stage, and histological subtype), reducing the major clinical and demographic bias in the survival analysis.

In summary, our study provided further evidence that male patients with breast cancer have lower long-term survival rates than women in China, particularly younger patients and those at an early clinical stage. Future studies with more detailed clinical treatment, cancer subtype, and lifestyle information are needed to deepen the understanding of male breast cancer biology and identify the factors that could eliminate this sex disparity.

Declarations

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Conflicts of interest/Competing interests: All authors declare that they have no conflicts of interest.

Availability of data and material: The data that support the findings of this study are available on request from the corresponding author (C.F.). The data are not publicly available due to privacy and ethical restrictions.

Code availability: The code that support the findings of this study are available on request from the corresponding author (Y.Z.).

Authors' contributions: Conception and design: Y.Z. and C.F.; Development of methodology: X. F., M.M, C.W.; Acquisition of data: C.W., M.G, C.F.; Analysis and interpretation of data: X. F., M.M, C.W.; Writing, review, and/or revision of the manuscript: all authors.; Study supervision: Y.Z. and C.F.

Ethics approval and consent to participate: The data used in this study were derived from a de-identified SCR database, and thus this study was exempt from the Institutional Review Board approval.

Consent for publication: NA.

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Tables

Table 1. Characteristics of male patients and female breast cancer patients diagnosed during 2002-2013 in Shanghai, China

Characteristics	Men	Matched women	All women	*P#*
N	434	1,736	50,524	
Age at diagnosis (Mean ± SD)	66.06 (13.44)	65.91 (13.34)	57.27 (12.87)	*<0.01*
Age group, year (N, %)				*<0.01*
<50	50 (11.52)	201 (11.58)	15,120 (29.93)	
50-59	90 (20.74)	376 (21.66)	16,527 (32.71)	
60-69	92 (21.20)	374 (21.54)	9,096 (18.00)	
70-79	130 (29.95)	513 (29.55)	6,680 (13.22)	
≥80	72 (16.59)	272 (15.67)	3,101 (6.14)	
Diagnosed year (N, %)				0.057
2002-2005	148 (34.10)	592 (34.10)	14,599 (28.90)	
2006-2009	130 (29.95)	520 (29.95)	16,614 (32.88)	
2010-2013	156 (35.94)	624 (35.94)	19,311 (38.22)	
TNM stage (N, %)				*<0.01*
I	79 (18.20)	316 (18.20)	12,428 (24.60)	
II	88 (20.28)	352 (20.28)	15,543 (30.76)	
III	40 (9.22)	160 (9.22)	4,493 (8.89)	
IV	31 (7.14)	124 (7.14)	3,244 (6.42)	
Unknown	196 (45.16)	784 (45.16)	14,816 (29.32)	
Histology (N, %)				*<0.01*
Infiltrating ductal carcinoma	236 (54.38)	944 (54.38)	35,718 (70.70)	
Others	83 (19.12)	332 (19.12)	6,279 (12.43)	

Unknown	115 (26.50)	460 (26.50)	8,527 (16.88)	
Vital status (N, %)				
Dead	231 (53.23)	683 (39.34)	15,576 (30.83)	*<0.01*
Dead due to cancer	196 (45.16)	556 (32.03)	13,627 (26.97)	*<0.01*
Without any follow-up (N, %)	0(0)	0(0)	18 (0.036)	
Cases recognized by death certificate only (N, %)	0(0)	0(0)	35 (0.069)	

[#] *P* value for the difference between men and all women breast cancer cases.

Table 2. 5-year observed overall survival (OS) and cancer-specific survival (CSS) rates of male and matched female breast cancer patients diagnosed during 2002-2013 by different characteristics

	5-year OS		5-year CSS	
Characteristics	**Men**	**Women**	**Men**	**Women**
ALL	67.27 (62.57-71.51)	77.75 (75.70-79.66)	70.19 (65.52-74.35)	79.79 (77.79-81.64)
Age group				
<70 years	79.57 (73.69-84.28)	88.69 (86.47-90.56)	80.65 (74.81-85.27)	89.39 (87.22-91.21)
≥70 years	52.78 (45.59-59.45)	64.58 (61.09-67.85)	57.48 (50.13-64.14)	68.04 (64.58-71.25)
TNM Stage				
I-II	84.99 (78.44-89.68)	90.86 (88.34-92.86)	86.75 (80.40-91.16)	93.28 (91.05-94.97)
III-IV	50.24 (37.89-61.37)	62.98 (57.01-68.37)	52.10 (39.50-63.29)	65.78 (59.79-71.11)
Unknown	57.31 (50.03-63.93)	69.66 (66.28-72.78)	62.45 (55.10-68.95)	73.69 (70.41-76.67)
Diagnosed year				
2002-2005	58.11 (49.74-65.58)	75.42 (71.73-78.69)	62.11 (53.58-69.52)	78.02 (74.43-81.17)
2006-2009	72.72 (64.13-79.59)	78.91 (75.13-82.18)	74.03 (65.46-80.78)	80.63 (76.92-83.80)
2010-2013	70.87 (62.78-77.51)	78.22 (74.64-81.35)	73.90 (65.91-80.30)	80.03 (76.54-83.06)
Histology				
IDC	75.62 (69.52-80.67)	84.55 (82.03-86.74)	77.43 (71.39-82.35)	85.56 (83.10-87.69)
Other	66.25 (54.74-75.48)	84.06 (79.61-87.61)	70.46 (58.92-79.32)	87.01 (82.83-90.23)
Unknown	48.98 (39.51-57.78)	57.30 (52.59-61.72)	52.97 (43.21-61.80)	60.97 (56.23-65.36)

Table 3. 10-year observed overall survival (OS) and cancer-specific survival (CSS) rates of male and matched female breast cancer patients diagnosed during 2002-2009 by different characteristics

	10-year OS		10-year CSS	
Characteristics	**Men**	**Women**	**Men**	**Women**
ALL	45.95 (39.85-51.82)	62.60 (59.62-65.42)	50.57 (44.27-56.53)	67.20 (64.26-69.96)
Age group				
<70 years	64.51 (55.85-71.90)	81.83 (78.41-84.77)	66.96 (58.32-74.21)	83.61 (80.28-86.42)
≥70 years	25.31 (18.10-33.14)	40.79 (36.46-45.07)	30.72 (22.44-39.37)	46.89 (42.30-51.35)
TNM Stage				
I-II	64.57 (53.91-73.37)	83.95 (79.77-87.34)	69.31 (58.68-77.72)	87.08 (83.16-90.14)
III-IV	26.75 (15.19-39.75)	45.61 (38.62-52.31)	27.05 (15.21-40.35)	49.75 (42.45-56.61)
Unknown	37.81 (29.23-46.34)	53.42 (48.93-57.71)	43.52 (34.20-52.47)	57.22 (52.62-61.55)
Diagnosed year				
2002-2005	41.08 (33.10-48.88)	62.08 (58.00-65.89)	43.91 (35.56-51.94)	65.55 (61.47-69.32)
2006-2009	47.92 (38.40-56.80)	61.87 (57.37-66.05)	57.04 (47.38-65.58)	67.88 (63.46-71.89)
Histology				
IDC	56.36 (47.59-64.22)	68.76 (64.66-72.49)	59.89 (51.03-67.66)	75.11 (71.21-78.56)
Other	47.52 (34.26-59.64)	73.63 (67.47-78.81)	55.57 (41.46-67.56)	76.81 (70.72-81.79)
Unknown	23.15 (14.05-33.59)	41.73 (36.05-47.30)	25.73 (15.64-37.03)	45.81 (39.91-51.51)

Table 4. Cox proportional hazards regression analysis for the overall and cancer-specific survival of male patients *vs.* female patients

Characteristics	Patients	Death	HR (95% CI) for OS	Death	HR (95% CI) for CSS
Overall	434	231	1.65 (1.42-1.92)	196	1.70 (1.44-2.00)
Age subgroup					
<70 years	232	81	2.02 (1.54-2.63)	75	2.07 (1.57-2.74)
≥70 years	202	150	1.55 (1.29-1.88)	121	1.52 (1.23-1.88)
TNM subgroup					
TNM I-II	167	61	1.89 (1.40-2.56)	52	2.00 (1.44-2.79)
TNM III-IV	71	54	1.73 (1.26-2.39)	49	1.84 (1.31-2.59)
TNM unknown	196	116	1.52 (1.23-1.88)	95	1.52 (1.20-1.91)
Diagnosed year					
2002-2005	148	103	1.91 (1.52-2.40)	91	2.04 (1.59-2.60)
2006-2009	130	66	1.43 (1.08-1.90)	54	1.46 (1.07-1.99)
2010-2013	156	62	1.55 (1.15-2.07)	51	1.50 (1.09-2.07)
Histology					
IDC	236	103	1.50 (1.20-1.88)	86	1.61 (1.26-2.07)
Others	83	47	2.64 (1.84-3.79)	38	2.55 (1.71-3.80)
Unknown	115	81	1.51 (1.17-1.95)	72	1.53 (1.16-2.00)

Figures

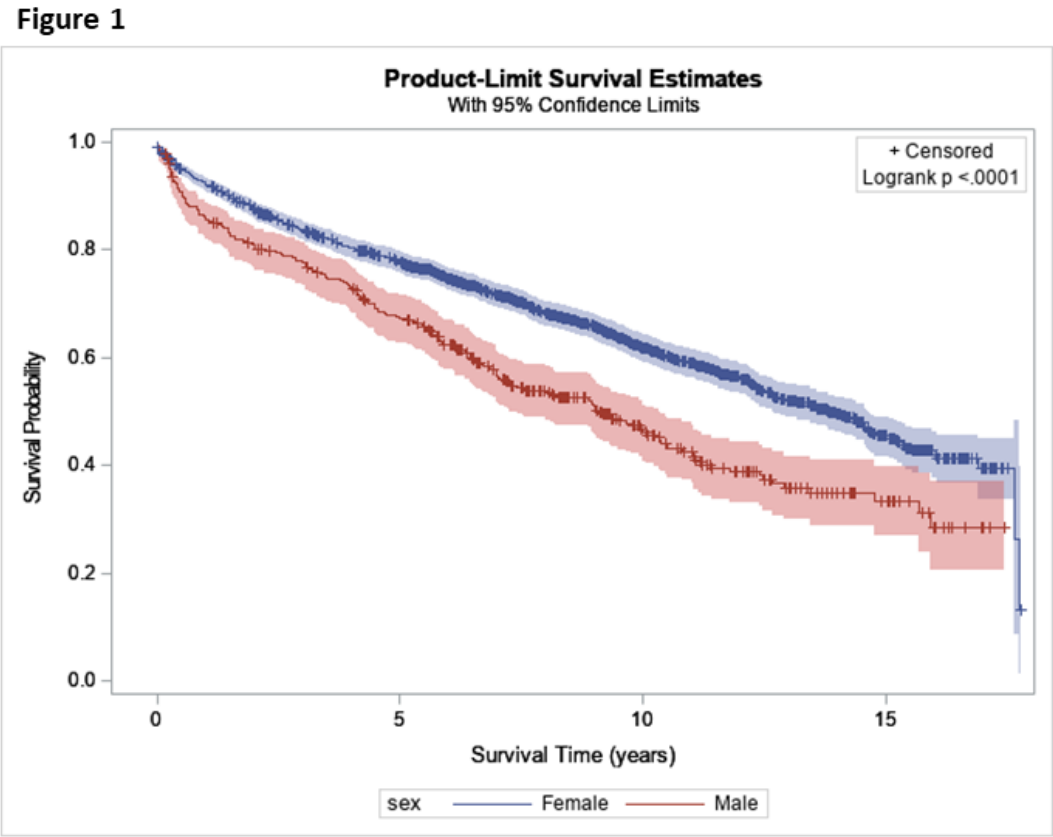

Figure 1

Observed overall survival of breast cancer patients diagnosed during 2002-2013 by sex.

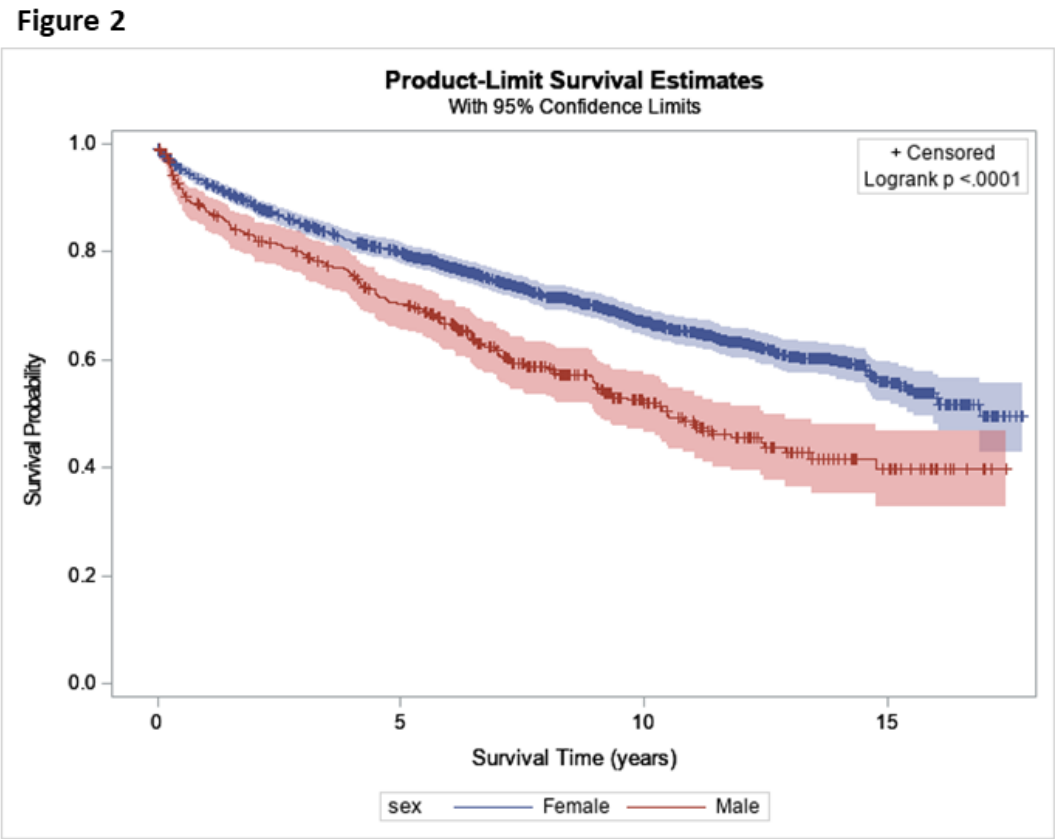

Figure 2

Cancer-specific survival of breast cancer patients diagnosed during 2002-2013 by sex.