Comparison of Male and Female Breast Cancer Incidence Trends, Tumor Characteristics, and Survival

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PURPOSE: To compare male and female breast cancer and to determine the predictors of tumor characteristics and survival in both genders.

METHODS: Male (n = 2923) and female breast cancer cases (n = 442,500) from the Surveillance, Epidemiology and End Results (SEER) registry were analyzed. Joinpoint regression was performed to detect changes in incidence trends from 1973 to 2001. Multiple logistic regression was used to regress each of four outcome variables (STAGE, LATERALITY, ESTROGEN, and PROGESTERONE RECEPTOR STATUS) on four demographic variables. Cox proportional hazards regression modeling was used to determine significant predictors of death of breast cancer after adjusting for demographic factors.

RESULTS: Both men and women aged less than 50 years were at higher risk for advanced breast cancers. Males were at higher risk than females for advanced tumors among non-whites. The risk of breast cancer death among all cases was lower for each 10-year increase in age by 2%, higher for those who are unmarried than for those who are married by 12% and 13% higher for non-whites than for whites.

CONCLUSIONS: Some important gender differences were detected with respect to factors associated with tumor characteristics, but gender was not a significant predictor of survival after adjusting for the other demographic variables.

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KEY WORDS: Breast Neoplasms Male, Breast Neoplasms Female, SEER Program, Survival, Epidemiology, Hormone Receptor.

INTRODUCTION

The epidemiology of female breast cancer is the topic of numerous research projects and manuscripts each year. Since there are over 215,000 new cases of breast cancer in women annually in the United States alone, case ascertainment is not a barrier to the conduct of epidemiologic studies—both descriptive and analytical. In men, however, there will only be an estimated 1450 annual incident cases of breast cancer in the U.S. in 2004 (1). Due to the rarity of breast carcinoma in men, much of the research—based on case series with relatively small samples—has focused on prognosis and genetic factors (2–7).

International population-based descriptive analyses, such as reports from Israel (n = 187) (8), Scandinavia (n = 1529) (9), central Italy (n = 32) (10), and Iceland (n = 31) (11) have reported comparable findings with respect to male breast cancer incidence (it is rare—less than 1 per 100,000 per year) and the mean age (male cases are, on average, half a decade older than female cases). However, most of our knowledge on the etiology of male breast cancer has been extrapolated from these small studies, underscoring the importance of determining similarities and differences between male and female breast cancer (12, 13). More recently, a study of gender- and age-specific incidence rate curves by Anderson et al. (14) reported stable incidence rates among men, compared with increasing trends among women. A comparison of prognostic factors led to the conclusion that male breast cancer is more similar to postmenopausal female breast cancer than premenopausal breast cancer (14).

Two recent studies have reported findings related to male breast cancer survival (15, 16). Atalay et al. (15) reported an overall 73% 5-year survival and 45% disease-free survival among men diagnosed with breast cancer. A study by El-Tamer et al. (16) compared male breast cancer survival with that of women and found that men had better disease-specific survival. However, it should be noted that small sample sizes were a limitation of both studies: the Atalay study included 55 male breast cancer patients from a single hospital; the El-Temar study was based on 53 male patients and 53 matched female controls.

The purpose of this study was to use data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute to describe the
epidemiology of male breast cancer, to compare gender- and race-specific incidence trends, and to determine if demographic factors and/or tumor characteristics are associated with disease-specific survival of breast cancer in men or women.

METHODS

Study Population

Cases included 2923 male breast cancer cases submitted to the 11 population-based cancer registries participating in the SEER Program from 1973 to 1999 (17). Gender comparisons use the 442,500 female breast cancer cases submitted to these registries during the same time interval. Additional cases (2000–2001) became available during the review of this manuscript and were included in the time trend analyses using joinpoint regression (JR) (18). Covering approximately 26% of the US population, the SEER Program routinely collects data on patient demographics, primary tumor site, morphology, stage at diagnosis, and follow-up for vital status. For those patients having more than one primary breast cancer diagnosis, the first instance of breast cancer was selected.

Statistical Methods

Breast cancer incidence trends. Joinpoint regression was performed to provide the estimated annual percentage change (EAPC) and to detect points in time where significant changes in trends occurred (19–21). The corresponding 95% confidence interval (CI) for each EAPC was also calculated. The JR model describes continuous changes in incidence rates and uses the grid-search method to fit the regression function with unknown joinpoints. The annual age-adjusted rates from 1973 to 2000 are examined and the points in time when the direction of the trends changes significantly are detected.

Univariate analysis. Unadjusted frequencies by gender were estimated for demographic variables and tumor characteristics using SPSS version 10.0 software (22). Inferential statistics are not presented for univariate comparisons, since the large number of comparison cases leads to consistent significant findings (even for extremely small observed differences).

Multivariate analysis. Multivariate analyses were performed using SAS version 9.0 software (23). All inferences were made at the 0.05 level of significance. Multiple logistic regression modeling was used to regress each of four outcome variables—STAGE, LATERALITY, ER (Estrogen Receptor) STATUS, and PR (Progesterone Receptor) STATUS—on four demographic variables (AGE, MARITAL STATUS, GENDER, and RACE). Each demographic variable was dichotomized: AGE (< 50, ≥ 50), MARITAL STATUS (Married, Not married) and RACE (White, Non-white). Four logistic regressions were performed, one for each outcome. In each case, a backward selection procedure was used to identify those demographic variables that had a significant effect on the outcome variable.

Survival time was analyzed for each of four predictors (STAGE, LATERALITY, ER STATUS, and PR STATUS) after adjusting for demographic variables (AGE, MARITAL STATUS, GENDER, and RACE). AGE was treated as a continuous variable, MARITAL STATUS was dichotomized (Married, Not married), and RACE was dichotomized (White, Non-white). The Cox proportional hazards regression model was used to compare the survival rate between the two levels of each predictor variable after adjusting for the demographic factors. The proportional hazards assumption was tested using Cox’s test, including interaction terms involving the covariates and log(t), where t = time variable; the interaction terms were tested for statistical significance (significance implying violation of the proportional hazards assumption).

RESULTS

Incidence

The incidence rate of male breast cancer (1992–1999) is 1.2 per 100,000 compared with 150.1 per 100,000 among women, indicating that approximately 1 out of every 150 breast cancers occurs in a male. JR analysis resulted in the trends displayed in Fig. 1. Among men of all ages, a significant 4.8% decrease in incident rates was noted from 1973 to 1977 (95% CI, −9.8 to 0.5). Since then—beginning in 1978—men have experienced a 1.2% increase (95% CI, 0.7 to 1.8) in breast cancer incidence. There were too few cases in the subcategories “non-white” and “< 50” to determine if significant race and/or age differences exist in males. By contrast, the large number of female cases allowed for age- and race-specific trends to be determined. White women aged less than 50 years experienced a 1.3% decline from 1973 to 1979 (95% CI, −2.5 to −0.1) followed by a 2.8% increase from 1980 to
1985 (95% CI, 0.8 to 4.9) and another decrease beginning in 1986 EAPC \( Z \) 0.3; 95% CI, 0.7 to 0.1). Only a single trend—a significant 0.5% increase—was detected during the entire time interval among non-white females aged less than 50 years (95% CI, 0.2 to 0.9). The racial differences in breast cancer incidence rates over time are more pronounced among women aged 50 years and older. Among white women in this group, a slight 0.1% decrease (95% CI, 1.3 to 1.1) was followed by a significant 4.2% increase (95% CI, 2.6 to 5.9) beginning in 1980 and a continued (although smaller) 0.6% increase (95% CI, 0.2 to 1.1) since 1987. Non-white women aged 50 years and older have experienced increasing incidence rates since 1973, with three trends emerging: a slight 0.2% increase from 1973 to 1980 (95% CI, 1.4 to 1.9) followed by a 5.4% increase for 5 years (95% CI, 0.5 to 10.6) and a 1.1% increase (95% CI, 0.4 to 1.7) beginning in 1986. The decreasing rates noted during the early- to mid-1970s are difficult to interpret; the early trend may stem from data quality issues or the fact that the SEER Program was less representative of the U.S. population during the early years.

Demographic and Tumor Characteristics by Gender

The demographic characteristics of male breast cancer cases are presented in Table 1. The distribution of female characteristics is shown for comparison. The mean age at diagnosis of male breast cancer was 64.8 years (SD = 13.0). Men were, on average, 4 years older at the time of diagnosis compared with women, whose mean age was 60.9 years (SD = 14.5). Compared with women, a lesser proportion of men were aged less than 50 years at the time of diagnosis (13.0% vs. 24.7%) and widowed (8.9% vs. 21.7%); a greater proportion of men were black (11.2% vs. 7.8%) and married (71.8% vs. 57.8%). Note the variable MARITAL STATUS has separate categories for Separated, Divorced, and...
Widowed. Therefore, "Married" should be interpreted as "Currently married/spouse is alive" throughout this article.

Tumor characteristics among men and women are presented in Table 2. Although the proportions of cases diagnosed as in situ tumors among males (12%) and females (16%) were relatively similar, localized invasive disease was more frequently diagnosed among women (54%) compared with men (46%) resulting in greater frequency of regional and advanced breast cancer in males (42%) than females (30%). The proportion of advanced cases (i.e., stage at diagnosis = regional or distant) by gender were clustered by 5-year intervals to discern any trend(s) over time; these proportions are presented in Fig. 2. Prior to 1980, the proportion of tumors that were "advanced" was similar in men (48.0%) and women (47.7%). Over the past 20 years, the proportion of advanced tumors has remained steady in men but has decreased in women. This gender difference becomes more pronounced over time as the effects of screening mammography become apparent. Since morphology coding standards have evolved over the years, this analysis of histological type and behavior uses breast cancer cases diagnosed between 1992 and 1999. The most frequent histologic type/behavior in men was ductal carcinomas (65.3%) followed by adenocarcinomas (15.4%). In women, the most common type/behaviors were also ductal carcinomas (64.9%) followed by in situ tumors (11.1%). Tumor marker data were available for over half of all male and female breast cancer cases, beginning in 1990. Males had a higher percentage of ER \(^+\) tumors (90.2%) compared with women (75.7%). Males also have a higher percentage of PR \(+\) tests (79.4%) compared with women (65.9%).

### Multivariate Analysis: Factors Associated with Tumor Characteristics

The results are given for each tumor characteristic (i.e., outcome variable) separately. The estimated odds ratios (ORs) are provided in Table 3 only for those results corresponding to statistically significant effects. All analyses are adjusted for the effects of the demographic variables.

#### Stage

STAGE was dichotomized (Advanced, Not advanced), where "Advanced" corresponds to "Regional/Distant" and "Not advanced" corresponds to "In situ/Localized." Logistic regression modeled the odds of "Advanced" STAGE. Among whites, those aged less than 50 years have a higher percentage of ER \(^+\) tumors (90.2%) compared with women (75.7%). Males also have a higher percentage of PR \(+\) tests (79.4%) compared with women (65.9%).

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#### TABLE 2. Tumor characteristics of male and female breast cancer cases, SEER Program (1973–1999)

<table>
<thead>
<tr>
<th>Stage at diagnosis</th>
<th>Males n = 1,400*</th>
<th>Females n = 222,299*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>1,350 (96.4)</td>
<td>216,446 (97.4)</td>
</tr>
<tr>
<td>In situ</td>
<td>157 (11.6)</td>
<td>33,928 (15.7)</td>
</tr>
<tr>
<td>Localized</td>
<td>622 (46.1)</td>
<td>116,898 (54.0)</td>
</tr>
<tr>
<td>Regional</td>
<td>486 (36.0)</td>
<td>55,012 (25.4)</td>
</tr>
<tr>
<td>Distant</td>
<td>85 (6.3)</td>
<td>10,608 (4.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laterality</th>
<th>Males n = 2,923</th>
<th>Females n = 442,500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>2,875 (98.4)</td>
<td>438,020 (99.0)</td>
</tr>
<tr>
<td>Right</td>
<td>1,401 (47.9)</td>
<td>213,226 (48.7)</td>
</tr>
<tr>
<td>Left</td>
<td>1,467 (50.2)</td>
<td>223,363 (51.0)</td>
</tr>
<tr>
<td>One only, unspecified</td>
<td>6 (0.2)</td>
<td>619 (0.1)</td>
</tr>
<tr>
<td>Bilateral involvement</td>
<td>1 (0.0)</td>
<td>812 (0.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histologic type/behavior</th>
<th>Males n = 1603**</th>
<th>Females n = 253,614**</th>
</tr>
</thead>
<tbody>
<tr>
<td>All in situ tumors</td>
<td>279 (9.5)</td>
<td>49,039 (11.1)</td>
</tr>
<tr>
<td>Adenocarcinomas</td>
<td>450 (15.4)</td>
<td>38,360 (8.7)</td>
</tr>
<tr>
<td>Comedocarcinomas</td>
<td>10 (0.3)</td>
<td>6,995 (1.6)</td>
</tr>
<tr>
<td>Ductal carcinomas</td>
<td>1,909 (65.3)</td>
<td>287,057 (64.9)</td>
</tr>
<tr>
<td>Lobular carcinomas</td>
<td>29 (1.0)</td>
<td>27,044 (6.1)</td>
</tr>
<tr>
<td>Paget's Disease</td>
<td>37 (1.3)</td>
<td>3,701 (0.8)</td>
</tr>
<tr>
<td>Other</td>
<td>209 (7.2)</td>
<td>30,304 (6.8)</td>
</tr>
</tbody>
</table>

*1992+ cases were selected; breast cancer stage of diagnosis is greatly impacted by screening mammography rates, which have increased dramatically over the past two decades.

**Tumor marker data available beginning in 1990.
years were at higher risk for being diagnosed at an advanced stage for women only. Among nonwhites, AGE (< 50), MARITAL STATUS (not married), and GENDER (male) were significant predictors of advanced breast cancer.

LATERALITY. LATERALITY was dichotomized (Right, Left). None of the demographic variables reached clinical significance in this model (Table 3).

Tumor markers. ER STATUS was dichotomized (ER C, ER/C). Logistic regression modeled the odds of “ER C.” “Age over 50” was associated with ER C STATUS among whites and non-whites as well as those who were married and not married (see Table 3). PR STATUS was dichotomized into (PR +, PR –) and logistic regression modeled the odds of “PR +.” Among whites, men and those aged more than 50 years were more likely to be PR +. These characteristics were not predictive of PR STATUS among non-whites (see Table 3).

Multivariate Analysis: Predictors of Breast Cancer Survival
An initial Cox regression analysis was used to determine which of the demographic variables had a significant effect on survival. The analysis revealed that AGE (RR = 0.998; 95% CI, 0.997 to 0.998), MARITAL STATUS (RR = 1.21; 95% CI, 1.19 to 1.23), and RACE (RR = 1.13; 95% CI, 1.11 to 1.16) all had a significant effect on survival (p < 0.0001 in each case). Specifically, the risk of breast cancer death is 1) lower for each 10-year increase in age by 2%, 2) higher for those who are not married by 21%, and 3) higher for non-whites by 13%. GENDER did not have a significant effect on survival (RR = 0.926; CI, 0.84 to 1.02). If we consider that a 10 percentage point change in risk of breast cancer death is of clinical importance, then MARITAL STATUS and RACE both have statistically and clinically significant effects on breast cancer survival. Each of the predictors, STAGE, LATERALITY, ER STATUS, and PR STATUS were then analyzed for their effects on survival after adjusting for the demographic factors. STAGE had a significant effect on survival rate (RR = 4.23; 95% CI, 4.16 to 4.29). As expected, tumor stage at the time of diagnosis has a significant effect on the risk of death from breast cancer. LATERALITY did not have a significant effect on survival rate (p = 0.3285). The hazard functions were nearly the
same for the two groups (RR = 1.008; 95% CI, 0.99 to 1.02). ER STATUS was found to have a significant effect on survival rate (RR = 1.9; 95% CI, 1.86 to 1.95). Our results suggest that the risk of death from breast cancer in patients with an ER− tumor is 90% higher compared with patients with an ER+ tumor. Our analysis also showed that PR STATUS had a significant effect on survival rate (RR = 1.94; 95% CI, 1.90 to 1.99); the risk for death from breast cancer in patients with a PR− tumor was almost double that of patients with a PR+ tumor.

**Survival Curves**

Unadjusted 5-year male breast cancer stage-specific survival rates are presented in Fig. 3. The female survival curves are shown for comparison. Similar curves were reviewed for each of the predictor variables (not shown). Survival (from breast cancer death) at a given time point tended to be higher for “not advanced” STAGE than for “Advanced” STAGE, about the same for “Right” and “Left” LATERALITY, higher for “ER+” than for “ER−”, and higher for “PR+” than for “PR−.” These results were in general agreement with the results based on the hazard functions.

**DISCUSSION**

For every 150 cases of female breast cancer, there is one case of male breast cancer. Since the late 1970s, there has been a single trend—a slight, 1.2% increase in male breast cancer incidence (both white and non-white, all ages), with observed values ranging from 0.5 to 1.6/100,000/year. Among women, there was a significant difference in rates between premenopausal and postmenopausal women. The ranges of rates for both whites and non-white premenopausal women have been quite similar over the past two decades, ranging from 35 to 47/100,000/year. The main difference seen among this group lies in the trend over the past decade, which is decreasing among whites but increasing among non-whites. Although the increasing trends for whites and non-whites are parallel for postmenopausal women, there is an observable difference in the actual range of rates.

**FIGURE 3.** Five-year breast cancer survival trends, SEER Program (1973–1999).
Specifically, white women aged 50 years and older have experienced higher incidence rates than their non-white counterparts (maximum observed rates—both occurring in 1999—were 410 and 315/100,000/year, respectively).

Unlike female breast cancer, there has been little change over the past couple of decades with respect to stage at diagnosis among male cases. The impact of screening mammography in the female population is apparent when the proportion of advanced tumors by gender is evaluated over time (Fig. 2). Prior to 1980, there is no significant effect of gender on the proportion of tumors that have reached an advanced stage at the time of diagnosis. Results of the National Health Interview Surveys, conducted in 1987, 1992, and again in 1998 found that the percent of women who had received a mammogram within the past 2 years has more than doubled since the first survey (28.8% in 1987 vs. 66.9% in 1998) (24). As expected, there is a decreasing trend in the proportion of advanced tumors in women, corresponding with an increase in mammographic screening, while the trend among men does not demonstrate a marked decrease in incidence at the advanced stages.

Because of the enormous sample size of 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 for one level of a demographic variable than another. In addition, the sample sizes for the different demographic subgroups vary widely. The number of females (n = 442,500) is substantially higher than the number of males (n = 2923), the number of whites (n = 382,078) is higher than the number of non-whites (n = 63,345), and the number whose age is under 50 years (n = 109,720) is lower than the number over 50 years (n = 335,703). For purposes of discussion, we define a result to be clinically significant if: 1) it is statistically significant at the 0.05 level of significance, and 2) the 95% CI for the odds ratio includes only values less than 0.9 or greater than 1.1 (i.e., the odds between two levels of a demographic variable change by at least 10 percentage points with 95% confidence).

The multivariate analyses of factors associated with tumor characteristics revealed significant findings among different gender-race subgroups. Among white females, the odds of being diagnosed at an advanced stage (i.e., regional or distant) were 21% higher for those aged less than 50 years compared with those aged more than 50 years (presumably as a result of screening mammography in the older group). Among non-whites, the odds of being diagnosed at an advanced stage are 80% higher for males compared with females; 26% higher for those aged less than 50 years than for those aged more than 50 years; and 15% lower for those who are married than for those who are not married. For each demographic subgroup, age—but not gender—was associated with ER STATUS. Specifically, the odds of ER+ were lower for those aged less than 50 years than for those aged more than 50 years. To summarize the findings with respect to factors associated with tumor characteristics, those aged less than 50 years are at higher risk than those aged more than 50 years for advanced stage breast cancers. The results also indicate that males are at higher risk than females for advanced-staged tumors among non-whites.

Table 3 also summarizes the risk factors associated with an increased risk of breast cancer death (i.e., decreased survival). The most notable finding was that gender was not a significant predictor of survival after adjusting for the other variables, including STAGE AT DIAGNOSIS. This finding supports some reports from smaller case series and gender comparison studies (13, 25) but is in disagreement with the more recent publication by El-Tamer et al. (16) that reported better survival among men compared with matched female controls. While gender was not predictive of breast cancer death, some demographic variables did yield significant findings. In terms of clinically relevant predictors (as defined earlier), those with breast cancers diagnosed at advanced stages are at more than quadruple the risk of dying from the disease compared with those with earlier-staged tumors. Those with PR− status are at nearly double the risk of breast cancer death compared with PR+ individuals. Similarly, those with ER− status are at nearly double the risk of breast cancer death compared with those who tested ER+.

While breast cancer in men is rare, an important step towards understanding (and eventually preventing) the disease is to describe the epidemiology of these tumors in a large population, relative to cases for which we have a better understanding (i.e., female breast cancer tumors). Although some important gender differences were detected with respect to factors associated with tumor characteristics, gender was not a significant predictor of survival after adjusting for the other demographic variables. Our main recommendation for future study is a large-scale analysis of gender-specific survival, including treatment variables in addition to the demographic factors in the current study.

REFERENCES


