Male Breast Cancer: A Population-Based Comparison With Female Breast Cancer

William F. Anderson, Ismail Jatoi, Julia Tse, and Philip S. Rosenberg

ABSTRACT

Purpose

Because of its rarity, male breast cancer is often compared with female breast cancer.

Patients and Methods

To compare and contrast male and female breast cancers, we obtained case and population data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program for breast cancers diagnosed from 1973 through 2005. Standard descriptive epidemiology was supplemented with age-period-cohort models and breast cancer survival analyses.

Results

Of all breast cancers, men with breast cancer make up less than 1%. Male compared with female breast cancers occurred later in life with higher stage, lower grade, and more estrogen receptor-positive tumors. Recent breast cancer incidence and mortality rates declined over time for men and women, but these trends were greater for women than for men. Comparing patients diagnosed from 1996 through 2005 versus 1976 through 1985, and adjusting for age, stage, and grade, cause-specific hazard rates for breast cancer death declined by 28% among men ($P = .03$) and by 42% among women ($P \approx 0$).

Conclusion

There were three intriguing results. Age-specific incidence patterns showed that the biology of male breast cancer resembled that of late-onset female breast cancer. Similar breast cancer incidence trends among men and women suggested that there are common breast cancer risk factors that affect both sexes, especially estrogen receptor-positive breast cancer. Finally, breast cancer mortality and survival rates have improved significantly over time for both male and female breast cancer, but progress for men has lagged behind that for women.

J Clin Oncol 28:232-239. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Male breast cancer makes up less than 1% of all cancers in men and less than 1% of all breast cancers in the United States.¹ Because of its rarity, comparatively little is known about its etiology, and there have been no prospective randomized clinical trials of male breast cancer.^{2,3} Consequently, the management of breast cancer among men is generalized from the management of breast cancer in women.^{3,4} However, without evidence-based data to support this female-to-male extrapolation, epidemiologic comparisons become an alternative source of information.⁵ Therefore, to compare and contrast population-based incidence, mortality, and survival rates for male and female breast cancers, we examined breast cancer cases in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Database from 1973 through 2005.

Several groups have recently reported incidence and mortality trends for male versus female breast cancers,⁶⁻¹⁰ but these studies were not adjusted for age, period, or cohort effects that may differ by sex. For example, breast cancer develops at older ages among men than among women.¹¹ Furthermore, calendar-period effects (associated with changing screening and/or treatment practice patterns) and birth-cohort or generational effects (associated with lifestyle and/or varying cancer risk factors) can vary between men and women. In this study, we complemented standard epidemiologic methods with age-period-cohort models that accounted for differential age, period, and cohort effects by sex.

Additionally, breast cancer in men occurs with higher stage, possibly because of delayed breast cancer detection.^{8,12} Male breast cancers also are typically low grade and frequently hormone receptor-positive.¹³ Therefore, to compare

From the Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services; Breast Care Center, National Naval Medical Center, Uniformed Services University, Bethesda, MD; and Dartmouth College, Hanover, NH.

Submitted April 25, 2009; accepted August 13, 2009; published online ahead of print at www.jco.org on December 7, 2009.

Supported in part by the Intramural Research Program of the National Institutes of Health, National Cancer Institute.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: William F. Anderson, MD, MPH, Biostatistics Branch (BB), DHHS/NIH/NCI/Division of Cancer Epidemiology and Genetics (DCEG), EPS, Room 8036, 6120 Executive Blvd, Bethesda, MD 20892-7244; e-mail: wanderso@mail.nih.gov.

© 2009 by American Society of Clinical Oncology

0732-183X/10/2802-232/\$20.00

DOI: 10.1200/JCO.2009.23.8162

the survival experience in men versus women, we estimated the male-to-female hazard ratios of breast cancer death adjusted for age, stage, and tumor characteristics at diagnosis.

To our knowledge, this is one of the largest comparative studies of male versus female breast cancer. The effects of age, period, and cohort for male breast cancer were considered

for prior eras by Moolgavkar et al¹⁴ from 1951 through 1970 and by Ewertz et al¹⁵ from 1943 through 1982. More recently, Goodman et al¹⁶ compared male and female breast cancer in the North American Association of Central Cancer Registries (1996 to 2000) but did not analyze trends in incidence or survival.

Table 1. Male and Female Breast Cancer Cases (in situ and invasive) in SEER 9, 13, and 17 Registries Databases

Characteristic*	Male			Female			P for Heterogeneity†
Sample size	5,494			835,805			
Percent of total No. of patients	0.7			99.3			
Age, years							
Mean	65.8			61.3			≈ 0
SE of the mean	0.18			0.02			
Median	67			61			
Range	10-104			11-108			
Tumor size, cm							≈ 0
Mean	2.4			2.2			
SE of the mean	0.03			0.003			
Median	2.0			1.6			
Rate per 100,000	1.1			142.7			
SE	0.02			0.16			
Variable	No. of Patients	Rate	IRR	No. of Patients	Rate	IRR	
Age, years (1973)							
70+	2,323	6.58	1.00	260,993	477.47	1.00	≈ 0
50-69	2,497	2.58	0.39	377,660	356.83	0.75	
40-49	524	0.67	0.10	148,713	186.12	0.39	
< 40	150	0.04	0.01	48,439	13.89	0.03	
Race (1973)							
White	4,616	1.01	1.00	711,904	152.85	1.00	2.3 × 10 ⁻¹⁴
Black	611	1.02	1.01	67,945	103.44	0.68	
Other/unknown	267	—‡	—	55,956	—	—	
Tumor size, cm (1988+)							
≤ 2.0	2,005	0.48	1.00	351,891	82.35	1.00	≈ 0
> 2.0	1,618	0.39	0.81	189,961	44.45	0.54	
Other/unknown	1,871	—	—	293,953	—	—	
Lymph node status (1998+)							
Negative	1,836	0.44	1.00	316,406	74.04	1.00	≈ 0
Positive	1,348	0.32	0.73	156,921	36.72	0.50	
Other/unknown	2,310	—	—	362,478	—	—	
SEER historical stage (1973)							
In situ	555	0.11	1.00	121,909	21.5	1.00	≈ 0
Local	2,321	0.47	4.13	420,723	71.1	3.30	
Regional	2,036	0.41	3.66	225,161	38.7	1.80	
Distant	380	0.08	0.68	43,371	7.2	0.33	
Other/unknown	202	—	—	24,641	—	—	
Grade (1973)							
Low	2,242	0.39	1.00	320,711	54.44	1.00	.01
High	1,440	0.25	0.64	224,656	38.14	0.70	
Other/unknown	1,712	—	—	290,438	—	—	
Estrogen receptor (1990+)							
Positive	2,576	0.65	1.00	344,406	85.33	1.00	≈ 0
Negative	212	0.05	0.08	100,152	24.81	0.29	
Other/unknown	2,706	—	—	391,247	—	—	

NOTE. Patients were diagnosed during the years 1973 through 2005 (n = 841,299 breast cancer cases with 1,160,300,297 person-years of follow-up in the catchment areas of Surveillance, Epidemiology, and End Results (SEER) 17 active Tumor Registries. Age-standardized incidence rate overall (males + females) = 77.2 (standard error [SE], 0.09) per 100,000 person-years.

Abbreviations: IRR, incidence rate ratio, where a given characteristic is compared with a referent characteristic with an assigned IRR of 1.0.

*SEER did not collect all variables for all time periods. For example, SEER did not collect tumor size until 1988 forward (1988+), as indicated in parentheses following various characteristics. Rates per 100,000 man-years or woman-years were age adjusted to the 2000 US standard population. For each demographic and tumor characteristic, missing or unknown data were designated as "other/unknown" for descriptive purposes but were excluded from further analyses.

†P values denoted "≈ 0" indicate extremely high levels of statistical significance, ie, calculated P values are smaller than 10⁻¹⁵.

‡— indicates that the rate and/or IRR were not calculated.

PATIENTS AND METHODS

We obtained breast cancer incidence data (in situ + invasive) from SEER 9, 13, and 17 Registries Databases,¹⁷⁻¹⁹ for cases diagnosed from 1973 through 2005. The SEER 9 Tumor Registries cover Atlanta, GA; Connecticut; Detroit, MI; Hawaii; Iowa; New Mexico; San Francisco-Oakland, CA; Seattle-Puget Sound, WA; and Utah. The SEER 9 data set includes breast cancer cases diagnosed from 1973 through 2005 and covers approximately 10% of the US population. The SEER 13 Registries Database includes the SEER 9 Registries plus the Registries for Los Angeles and San Jose-Monterey, CA; rural Georgia; and the Alaskan Native Tumor Registry. The SEER 13 data set adds cases diagnosed from 1992 through 2005 and covers approximately 14% of the US population. The SEER 17 Registries Database includes the SEER 13 Registries plus Registries for Greater California, Kentucky, Louisiana, and New Jersey. The SEER 17 data set adds cases diagnosed from 2000 through 2005 and covers approximately 26% of the US population. Mortality data for SEER's 17 Tumor Registries was supplied by the National Center for Health Statistics (NCHS; 1969 through 2005).²⁰

Demographic and tumor characteristics included sex, age at diagnosis, race (white, black, and other/unknown), tumor size in centimeters, axillary lymph node status (positive *v* negative), SEER historic stage A, grade, and estrogen receptor (ER) expression (positive *v* negative). SEER historic stage A classified breast cancers as in situ (noninvasive), localized (invasive disease limited to the breast), regional (invasive disease limited to surrounding tissues), and distant or systemic disease. Tumor grade was dichotomized into low-grade (well differentiated plus moderately differentiated) and high-grade (poorly differentiated plus undifferentiated). For each demographic and tumor characteristics, missing or unknown data were designated as "other/unknown" for descriptive purposes but were excluded from further analyses. SEER collected demographic and tumor variables from 1973 forward, except for tumor size (1988 forward), lymph node status (1988 forward), and ER expression (1990 forward).

Age Standardized Rates

We calculated incidence and mortality age standardized rates (ASRs) using the 2000 US standard population. Relative risks for incidence were expressed as incidence rate ratios (IRRs), where a given characteristic was compared with a referent characteristic with an assigned IRR of 1.0. The null hypothesis of no difference by sex was assessed by χ^2 tests for heterogeneity. All hypothesis tests were two-sided. *P* values less than .05 were considered to be statistically significant. *P* values denoted by "*p* $\approx$ 0" indicate extremely high levels of statistical significance (ie, calculated *P* values smaller than 10^{-15}).

ASR incidence and mortality trends were plotted on a log-linear scale from 1974 through 2005, using eight 4-year calendar periods (1974 to 1977, 1978 to 1981, . . . , 2002 to 2005) such that a slope of 10 degrees approximated a change in rates of 1% per year.²¹ Temporal trends, from the beginning to the end of the study period, were quantified using the estimated annual percentage change (EAPC) of the ASR that was computed with weighted least squares log-linear regression.²²

Age-Period-Cohort Models

We fitted age-period-cohort (APC) models with eight 4-year calendar periods (1974 to 1977, 1978 to 1981, . . . , 2002 to 2005) and sixteen 4-year age groups (21 to 24, 25 to 28, . . . , 81 to 84),²³ spanning 23 nominal 8-year birth cohorts (1893, 1897, . . . , 1981; referred to by midyear of birth). For this analysis, we calculated two estimable quantities from our APC models: net drift and the fitted age-specific curves.²⁴⁻²⁸ Net drift is the sum of the linear trends in period and cohort effects. The net drift quantifies the average annual percentage change in the logarithm of the rates adjusted for period and cohort deviations across all age groups. It is a summary measure of the overall trend during the study period and is closely related to the EAPC of the ASR.²⁸

The fitted age-specific curve provides an estimate of the standard longitudinal age-specific rates, adjusted for period and cohort effects.^{27,28} We derived fitted age-specific curves separately for men and women so that period and cohort effects could vary freely by sex. Wald tests were used to compare the APC parameters between male and female breast cancers, as previously described.²⁷

Breast Cancer-Specific Survival

Actuarial breast cancer-specific survival rates with 95% CIs were calculated for males and females using the Kaplan-Meier method.²⁹ The Kaplan-Meier estimator treats all deaths from causes other than breast cancer as independent censoring events. We used Poisson regression to model hazard rates of breast cancer death adjusted for calendar period, age at diagnosis, and tumor characteristics.³⁰ Three calendar periods were chosen to estimate the likelihood of receiving adjuvant tamoxifen following the Nolvadex Adjuvant Trial Organization (NATO) interim analysis in 1983³¹: 1976 through 1985 (adjuvant tamoxifen not likely for either men or women), 1986 through 1995 (adjuvant tamoxifen likely for women but not for men), and 1996 through 2005 (adjuvant tamoxifen likely for men and women). Three age groups were chosen to approximate mammography screening prevalence among women: age younger than 50 years (low to no screening), age 50 to 69 years (likely screened), and age 70+ years (low to no screening). SEER did not record all tumor characteristics for the entire study period (Table 1); hence, the Poisson models were adjusted only for variables that were collected from 1973 forward, ie, age at diagnosis, SEER historic stage A (local, regional, or distant), and tumor grade (low or high). We also did not adjust for race because of the small sample sizes among blacks.

RESULTS

Descriptive Statistics

SEER's 9, 13, and 17 Registries Databases had a combined total of 841,299 in situ and invasive breast cancer cases with 1,160,300,297

Fig 1. Age-standardized rates (ASRs) with the estimated annual percentage changes (EAPCs) in the ASR for male and female (A) breast cancer incidence rates and (B) mortality rates. (A) ASR for incidence (in situ + invasive). From 1974 to 2005, EAPCs were 1.30% per year (95% CI, 0.97% to 1.62%) for women and 0.86% per year (95% CI, 0.47% to 1.25%) for men. ASRs peaked in 1999 at 165 per 100,000 for women, after which the EAPC fell at a rate of -1.85% per year (95% CI, -2.63% to -1.07%). ASRs peaked in 2000 at 1.24 per 100,000 for men, after which the EAPC was -0.46% per year (95% CI, -5.45% to 5.25%). (B) ASR for mortality: From 1974 through 2005, EAPCs were -1.16% per year (95% CI, -1.41% to -0.91%) for women and -0.27% per year (95% CI, -0.77% to 0.23%) for men.

person-years of follow-up among all people residing in the catchment areas of the active SEER Tumor Registries during the years 1973 through 2005. In situ breast cancers accounted for 10.1% (555 of 5,494) of breast cancers among men and 14.6% (121,909 of 835,805) of breast cancers among women. Males composed 0.65% ($n = 5,494$) of all breast cancer cases. Males compared with females had older age at diagnosis and larger tumor size. Age-standardized incidence rates overall were more than 100-fold lower for men than for women, ie, 1.1 (standard error, 0.02) versus 142.7 (standard error, 0.16) per 100,000 person-years.

Black-to-white incidence rate ratios (IRR_{BW}) were 1.01 for men and 0.68 for women (Table 1; $P = 2.3 \times 10^{-14}$). High-risk stage-related variables (larger tumor sizes and positive axillary lymph nodes) were more common among men than among women, whereas high-risk biologic characteristics (high grade and ER-negative disease) were more common among women. For example, $IRR_{\text{tumor size}}$ for more than 2.0 cm versus ≤ 2.0 cm was greater for males: 0.81 (95% CI, 0.76 to 0.86) for men and 0.54 (95% CI, 0.54 to 0.54) for women. In contrast, IRR_{ER} for ER-negative versus ER-positive disease was greater for females: 0.29 (95% CI, 0.29 to 0.29) for women and 0.08 (95% CI, 0.07 to 0.09) for men. In fact, 22.5% of female breast cancers with known ER expression were ER-negative (100,152 of 100,152 + 344,406) compared with 7.6% of male breast cancers (212 of 212 + 2,576). Consequently, 77.5% and 92.4% of breast cancers were ER-positive for women and men, respectively.

Secular trends in the ASR. The ASR (Fig 1) for incidence increased over time for both women and men (Fig 1A). The EAPC for

incidence rates was 1.30% per year (95% CI, 0.97% to 1.62%) for women and 0.86% per year (95% CI, 0.47% to 1.25%) for men. Incidence rates peaked in 1999 for women at 165 per 100,000 woman-years and in 2000 for men at 1.24 per 100,000 man-years. The ASR for mortality (Fig 1B) fell for women at an EAPC of -1.16% per year (95% CI, -1.41% to -0.91%) and for men at an EAPC of -0.27% per year (95% CI, -0.77% to 0.23%), but the decline was not statistically significant for men.

APC models. As shown in Figures 2 and 3, net drifts for incidence rates rose 1.19% per year for men (Fig 2A) and 1.48% per year for women (Fig 2B). Similar to the EAPCs for incidence (Fig 1A), net drifts for incidence did not differ by sex ($P = .38$). Also similar to EAPCs for incidence, age-specific incidence rates peaked near year 2000 for both men (Fig 2A) and women (Fig 2B). In contrast to similar EAPCs for incidence and to similar net drifts for incidence (Figs 1A and 2), net drifts for mortality differed by sex (Fig 3; $P = .046$), ie, -0.58% per year for men (Fig 3A) and -1.28% per year for women (Fig 3B). Age-specific mortality declined for all age groups among women (Fig 3B) and less so for men (Fig 3A).

The fitted age-at-onset curves for incidence and mortality that were adjusted for period and cohort effects were significantly different between men and women (Fig 4; $P \approx 0$). Among women (Fig 4A), incidence increased rapidly until around age 50 years, then slowed, after which rates rose at a slower pace. Among men (Fig 4A), incidence increased steadily with age. Given the slowing incidence rates among women and the steadily rising rates among men, the male-to-female IRRs moved closer to equality (ie, toward an $IRR_{MF} = 1.0$) with advancing age (Fig 4B). The pause in the female fitted age-at-onset

Fig 2. Age-specific incidence rate trends with the net drifts expressed as an annual percentage change for male (A) and female (B) breast cancer. Reference line is drawn at the year 2000 where incidence rates peaked for men and women. (A) Annual percentage change in the net drifts for male breast cancer incidence rates was 1.19% per year (95% CI, 0.54% to 1.83%). (B) Annual percentage change in the net drifts for female breast cancer incidence rates was 1.48% per year (95% CI, 1.34% to 1.63%).

Fig 3. Age-specific mortality rate trends with the net drifts expressed as an annual percentage change for male (A) and female (B) breast cancer. (A) Annual percentage change in the net drifts for male breast cancer mortality rates was -0.58% per year (95% CI, -1.27% to 0.11%). (B) Annual percentage change in the net drifts for female breast cancer mortality rates was -1.28% per year (95% CI, -1.34% to -1.22%).

Fig 4. Age-period-cohort fitted age-specific curves (A and C) and age-specific rate ratios (B and D) for male and female breast cancers. (A) The age-specific incidence rates among women increased rapidly until age 50 years and then paused, after which incidence rates rose at a slower pace. The age-specific inflection near age 50 years has been termed Clemmesen's hook. Clemmesen's hook has been attributed to menopause and is absent among men. Age-specific incidence rates for men rose steadily (linearly or monotonically) with aging and lacked a Clemmesen's hook. (B) Male-to-female age-specific incidence rate ratio narrowed steadily with advancing age. (C) Age-specific mortality rates among women increased rapidly until age 50 years and then paused near Clemmesen's hook, after which mortality rates rose at a slower pace. Age-specific mortality rates for men rose steadily (linearly or monotonically) with aging. (D) Male-to-female age-specific mortality rate ratio narrowed steadily with advancing age.

curve near 50 years has been termed Clemmesen's menopausal hook and is absent in age-at-onset curves for men.^{32,33}

The fitted age-specific mortality rates (Fig 4C) had patterns similar to the fitted age-specific incidence rates (Fig 4A). Among women (Fig 4C), age-specific mortality rates increased rapidly until around age 50 years, then slowed, after which rates rose at a slower pace. Among men (Fig 4C), the age-specific mortality rates increased steadily with age. Given the slowing age-specific mortality rates among women and the steadily rising rates among men, the male-to-female IRRs moved closer to 1.0 with advancing age (Fig 4D).

Breast Cancer Survival

During the entire study period, 16% of men and 16% of women with breast cancer died of their disease (863 of 5,494 male patients and 134,285 of 835,805 female patients). Kaplan-Meier plots showed a gradual improvement over time, which was more obvious for women (Fig 5B) than for men (Fig 5A). Hazard ratios for breast cancer death

adjusted for age, stage, and grade confirmed that the relative improvement over time was more modest for men (Fig 5C) compared with women (Fig 5D), and that the rate of improvement was slower for men compared with that for women. Specifically, for men (Fig 5C), adjusted hazard ratios fell by 28% ($P = .03$) from the 1976 to 1985 period to the 1996 to 2005 period. For women (Fig 5D), the hazard ratios fell by 42% ($P \approx 0$) over the same time period, with a 28% ($P \approx 0$) decline from the 1976 to 1985 period to the 1986 to 1995 period and another 14% decline from the 1986 to 1995 period to the 1996 to 2005 period ($P \approx 0$).

DISCUSSION

This large-scale population-based comparison between male and female breast cancers provided intriguing etiologic and prognostic clues. First, the similarity of both the age-standardized and age-specific incidence rate trends over time raises the possibility that there

Fig 5. Actuarial breast cancer-specific free survival (A and B) and hazard rates for breast cancer death (C and D) for male and female breast cancers, with 95% CIs. Hazard ratios for breast cancer death were adjusted for age at diagnosis, Surveillance, Epidemiology, and End Results (SEER) historic stage A (local, regional, or distant), and tumor grade (low and high). (A) Actuarial breast cancer-specific free survival for male breast cancer from 1976 to 1985, 1986 to 1995, and 1996 to 2005. (B) Actuarial breast cancer-specific free survival for female breast cancer from 1976 to 1985, 1986 to 1995, and 1996 to 2005. (C) Hazard rate ratios for male breast cancer deaths. Hazard rates during 1986 to 1995 and 1996 to 2005 were compared with a baseline hazard rate during 1976 to 1985. (D) Hazard rate ratios for female breast cancer deaths. Hazard rates during 1986 to 1995 and 1996 to 2005 were compared with a baseline hazard rate during 1976 to 1985.

may be breast cancer risk factors that are common to both men and women. Second, the descriptive patterns show that the biology of male breast cancer resembles the late-onset and ER-positive type of female breast cancer. Finally, mortality and survival rates for male and female breast cancers improved substantially over time, but progress in men lagged behind progress in women.

Clinicians have long suspected that there are at least two types of female breast cancer: the first is early-onset and premenopausal, whereas the second is late-onset and postmenopausal.^{14,34} A bimodal characterization also correlates well with the two main breast cancer biomarkers (ER and human epidermal growth factor receptor-2 [HER2]) and the two main molecular signatures (luminal and basal-like).³⁵⁻³⁷ If male breast cancer is more similar to the late-onset type of female breast cancer that has increased markedly over the last half century,³⁸ then some risk factors for late-onset breast cancer in men may be closely aligned with environmental exposures common to both men and women, rather than to the early-onset and female-specific risk factors such as hormonal exposures, reproductive variables, screening mammography, and so on. In other words, late-onset breast cancers in both sexes may be associated with long-term trends in environmental and/or other nonhormonal risk factors such as diet, obesity, and so on, whereas early-onset breast cancers are generally female-specific and somewhat uncommon in men.

Indeed, early-onset male breast cancers have been associated with Klinefelter's syndrome and *BRCA2* mutations, but they explain only a minority of all breast cancers among men. These cases occur nearly a decade earlier in life than typical male breast cancer (Table 1), eg, age 58 years for both Klinefelter's syndrome^{39,40} and *BRCA* mutations⁴¹ compared with age 67 years in SEER. Furthermore, in population-based series of male breast cancer, the prevalence of Klinefelter's syndrome and *BRCA2* mutations is 7.5%⁴² and 2% to 8%,^{41,43,44} respectively.

Declining female breast cancer mortality rates are attributed to adjuvant systemic therapy, screening mammography, and reductions in hormone replacement therapy usage.^{45,46} Any declines in male breast cancer mortality rates would likely reflect just the impact of adjuvant systemic treatments, since men receive neither screening mammography nor hormone replacement therapy. The efficacy of adjuvant hormonal therapy (mainly tamoxifen) for female breast cancer was shown in the NATO trial in 1983,³¹ and its effectiveness was subsequently demonstrated in the general population.^{45,47} However, there have been no population-based studies confirming the effectiveness of tamoxifen among men. This study is the first to suggest that male breast cancer mortality (Fig 3A) and survival rates (Fig 5C) have improved in the general population, especially after 1996.

Evidence-based guidelines for adjuvant systemic therapy in female breast cancer are rapidly implemented into community practice,⁴⁸ but the same may not be true for men. Indeed, the smaller improvement for male than for female hazard ratios suggest a delay and/or underutilization of adjuvant therapy in men compared with women, especially tamoxifen for hormone-positive male breast cancer.⁴⁹ Only 39% of men received tamoxifen in three Oregon-based hospital systems during 1986 to 1999, and most of these men were treated during the later time periods.⁵⁰ During the same time intervals, the vast majority of women received tamoxifen for hormone receptor-positive disease.⁴⁵ At the M.D. Anderson Cancer Center, 39% (13 of 33) and 63% (24 of 38) of men with breast cancer received adjuvant hormonal therapy during the 1980s and 1990s, respectively.⁵¹ Tamoxifen for male breast cancer may also be limited by poor compliance because it is associated with high rates of treatment-limiting side effects in men,⁵² eg, decreased libido, weight gain, hot flashes, deep venous thrombosis, and so on.

Our study has the usual limitations of descriptive epidemiology, that is, retrospective registry assessment, missing data in SEER, non-standardized definitions, and lack of individual-level risk factor data. Small sample sizes for some groups of male breast cancer patients such as black race were another limitation. Nonetheless, this is one of the largest comparative studies to date of male versus female breast cancers and an important source of information in the absence of randomized clinical trials for men. Another major strength was the supplementation of standard descriptive epidemiology with age-period-cohort models adjusted for period and cohort effects and survival analysis adjusted for age, stage, and grade.

Ultimately, a better molecular understanding of the differences between early-onset and late-onset breast cancers might help separate

potential environmental risk factors from those that are intrinsically female-specific. At the same time, additional translational studies are needed to better extrapolate the successful adjuvant treatments for female breast cancer to male breast cancer, especially hormonal treatments for hormone receptor-positive disease. However, given that there have been no randomized clinical trials regarding the efficacy of tamoxifen among men with breast cancer, this descriptive study is important because it provides population-based evidence that tamoxifen is likely effective in treating male breast cancer. Finally, a more comprehensive understanding of the secular as well as age-related relationships between male and female breast cancers will inform both the prevention and treatment of breast cancer overall.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: William F. Anderson, Ismail Jatoui, Julia Tse, Philip S. Rosenberg

Administrative support: William F. Anderson

Provision of study materials or patients: William F. Anderson, Julia Tse

Collection and assembly of data: William F. Anderson, Julia Tse

Data analysis and interpretation: William F. Anderson, Ismail Jatoui, Philip S. Rosenberg

Manuscript writing: William F. Anderson, Ismail Jatoui, Julia Tse, Philip S. Rosenberg

Final approval of manuscript: William F. Anderson, Ismail Jatoui, Julia Tse, Philip S. Rosenberg

REFERENCES

- Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2008. *CA Cancer J Clin* 58:71-96, 2008
- Tischkowitz MD, Hodgson SV, Fentiman IS: 19. Male breast cancer: Aetiology, genetics and clinical management. *Int J Clin Pract* 56:750-754, 2002
- Giordano SH: Male breast cancer: It's time for evidence instead of extrapolation. *Onkologie* 31: 505-506, 2008
- English JC 3rd, Middleton C, Patterson JW, et al: Cancer of the male breast. *Int J Dermatol* 39:881-886, 2000
- Berry DA, Ravdin PM: Breast cancer trends: A marriage between clinical trial evidence and epidemiology. *J Natl Cancer Inst* 99:1139-1141, 2007
- Hodgson NC, Button JH, Franceschi D, et al: Male breast cancer: Is the incidence increasing? *Ann Surg Oncol* 11:751-755, 2004
- Giordano SH, Cohen DS, Buzdar AU, et al: Breast carcinoma in men: A population-based study. *Cancer* 101:51-57, 2004
- Fentiman IS, Fourquet A, Hortobagyi GN: Male breast cancer. *Lancet* 367:595-604, 2006
- Stang A, Thomssen C: Decline in breast cancer incidence in the United States: What about male breast cancer? *Breast Cancer Res Treat* 112:595-596, 2008
- Contractor KB, Kaur K, Rodrigues GS, et al: Male breast cancer: Is the scenario changing. *World J Surg Oncol* 6:58, 2008
- Anderson WF, Althuis MD, Brinton LA, et al: Is male breast cancer similar or different than female breast cancer? *Breast Cancer Res Treat* 83:77-86, 2004
- Pant K, Dutta U: Understanding and management of male breast cancer: A critical review. *Med Oncol* 25:294-298, 2008
- Giordano SH, Buzdar AU, Hortobagyi GN: Breast cancer in men. *Ann Intern Med* 137:678-687, 2002
- Moolgavkar SH, Lee JA, Hade RD: Comparison of age-specific mortality from breast cancer in males in the United States and Japan. *J Natl Cancer Inst* 60:1223-1225, 1978
- Ewertz M, Holmberg L, Karjalainen S, et al: Incidence of male breast cancer in Scandinavia, 1943-1982. *Int J Cancer* 43:27-31, 1989
- Goodman MT, Tung KH, Wilkens LR: Comparative epidemiology of breast cancer among men and women in the US, 1996 to 2000. *Cancer Causes Control* 17:127-136, 2006
- SEER-9: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 9 Regs Limited-Use, Nov 2007 Sub (1973-2005) < Single Ages to 85+, Katrina/Rita Population Adjustment > -Linked To County Attributes - Total U.S., 1969-2005 Counties, National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch, released April 2008, based on November 2007 submission
- SEER-13: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 13 Regs Limited-Use, Nov 2007 Sub (1973-2005) < Single Ages to 85+, Katrina/Rita Population Adjustment > -Linked To County Attributes - Total U.S., 1969-2005 Counties, National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch, released April 2008, based on November 2007 submission
- SEER-17: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 17 Regs Limited-Use, Nov 2007 Sub (1973-2005) < Single Ages to 85+, Katrina/Rita Population Adjustment > -Linked To County Attributes - Total U.S., 1969-2005 Counties, National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch, released April 2008, based on November 2007 submission
- SEER: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Mortality - All Cause of Death, Total U.S. (1969-2005) < Single Ages to 85+, Katrina/Rita Population Adjustment > -Linked To County Attributes - Total U.S., 1969-2005 Counties, National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch, released February 2008. Underlying mortality data provided by the NCHS (www.cdc.gov/nchs), 2008
- Devesa SS, Donaldson J, Fears T: Graphical presentation of trends in rates. *Am J Epidemiol* 141:300-304, 1995

22. Kim HJ, Fay MP, Feuer EJ, et al: Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 19:335-351, 2000
23. Holford TR: The estimation of age, period and cohort effects for vital rates. *Biometrics* 39:311-324, 1983
24. Clayton D, Schifflers E: Models for temporal variation in cancer rates: II. Age-period-cohort models. *Stat Med* 6:469-481, 1987
25. Clayton D, Schifflers E: Models for temporal variation in cancer rates: I. Age-period and age-cohort models. *Stat Med* 6:449-467, 1987
26. Holford TR: Age-period-cohort analysis, in Armitage P, Colton T (eds): *Encyclopedia of Biostatistics*. Chichester, England, John Wiley & Sons, 1998, pp 82-99
27. Anderson WF, Rosenberg PS, Menashe I, et al: Age-related crossover in breast cancer incidence rates between black and white ethnic groups. *J Natl Cancer Inst* 100:1804-1814, 2008
28. Anderson WF: Cancer surveillance research. *Cancer Epidemiol Biomarkers Prev* 18:1669-1671, 2009
29. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
30. Breslow NE, Lubin JH, Marek P, et al: Multiplicative models and cohort analysis. *J Am Stat Assoc* 78:1-12, 1983
31. Controlled trial of tamoxifen as adjuvant agent in management of early breast cancer: Interim analysis at four years by Nolvadex Adjuvant Trial Organisation. *Lancet* 1:257-261, 1983
32. Clemmesen J: Carcinoma of the breast: Results from statistical research. *Br J Radiol* 21:583-590, 1948
33. Thomas DB: Breast cancer in men. *Epidemiol Rev* 15:220-231, 1993
34. de Waard F: Premenopausal and postmenopausal breast cancer: One disease or two? *J Natl Cancer Inst* 63:549-552, 1979
35. Perou CM, Sorlie T, Eisen MB, et al: Molecular portraits of human breast tumours. *Nature* 406:747-752, 2000
36. Sørlie T, Wang Y, Xiao C, et al: Distinct molecular mechanisms underlying clinically relevant subtypes of breast cancer: Gene expression analyses across three different platforms. *BMC Genomics* 7:127, 2006
37. Anderson WF, Pfeiffer RM, Dores GM, et al: Comparison of age frequency distribution patterns for different histopathologic types of breast carcinoma. *Cancer Epidemiol Biomarkers Prev* 15:1899-1905, 2006
38. Fox MS: On the diagnosis and treatment of breast cancer. *JAMA* 241:489-494, 1979
39. Evans DB, Crichlow RW: Carcinoma of the male breast and Klinefelter's syndrome: Is there an association? *CA Cancer J Clin* 37:246-251, 1987
40. Sasco AJ, Lowenfels AB, Pasker-de Jong P: Review article: Epidemiology of male breast cancer—A meta-analysis of published case-control studies and discussion of selected aetiological factors. *Int J Cancer* 53:538-549, 1993
41. Basham VM, Lipscombe JM, Ward JM, et al: BRCA1 and BRCA2 mutations in a population-based study of male breast cancer. *Breast Cancer Res* 4:R2, 2002
42. Hultborn R, Hanson C, Köpf I, et al: Prevalence of Klinefelter's syndrome in male breast cancer patients. *Anticancer Res* 17:4293-4297, 1997
43. Friedman LS, Gayther SA, Kurosaki T, et al: Mutation analysis of BRCA1 and BRCA2 in a male breast cancer population. *Am J Hum Genet* 60:313-319, 1997
44. Ottini L, Rizzolo P, Zanna I, et al: BRCA1/BRCA2 mutation status and clinical-pathologic features of 108 male breast cancer cases from Tuscany: A population-based study in central Italy. *Breast Cancer Res Treat* 116:577-586, 2009
45. Berry DA, Cronin KA, Plevritis SK, et al: Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med* 353:1784-1792, 2005
46. Ravdin PM, Cronin KA, Howlader N, et al: The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med* 356:1670-1674, 2007
47. Jatoi I, Chen BE, Anderson WF, et al: Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. *J Clin Oncol* 25:1683-1690, 2007
48. Mariotto A, Feuer EJ, Harlan LC, et al: Trends in use of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States: 1975-1999. *J Natl Cancer Inst* 94:1626-1634, 2002
49. Ribeiro G, Swindell R: Adjuvant tamoxifen for male breast cancer (MBC). *Br J Cancer* 65:252-254, 1992
50. Vetto J, Jun SY, Paduch D, et al: Stages at presentation, prognostic factors, and outcome of breast cancer in males. *Am J Surg* 177:379-383, 1999
51. Giordano SH, Perkins GH, Broglio K, et al: Adjuvant systemic therapy for male breast carcinoma. *Cancer* 104:2359-2364, 2005
52. Anelli TF, Anelli A, Tran KN, et al: Tamoxifen administration is associated with a high rate of treatment-limiting symptoms in male breast cancer patients. *Cancer* 74:74-77, 1994