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ORIGINAL REPORT

Improvement in Breast Cancer Outcomes Over Time: Are Older Women Missing Out?

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ABSTRACT

Purpose
Women aged ≥ 75 years account for 40,000 breast cancers/yr and are the most rapidly growing demographic. Recent data demonstrated that breast cancer death rates in the US population are declining, but it is not known whether death rates have declined similarly for older and younger women. We examined the following two outcomes: the rate of breast cancer death in the general population and the risk of breast cancer death in newly diagnosed patients, and we compared change over time in these outcomes for older versus younger women.

Methods
By using data from National Vital Statistics Reports that spanned from 1990 to 2007, the yearly change in the age-specific rate of breast cancer death was characterized with linear regression. With the use of the Surveillance, Epidemiology, and End Results nine-registry cohort that spanned from 1980 to 1997, the yearly change in age-specific risk of breast cancer death was characterized by using competing-risks regression adjusted for race and stage.

Results
Relative to 1990, the rate of breast cancer death in the general population decreased by 2.5%/yr for women age 20 to 49 years, 2.1%/yr for women age 50 to 64 years, 2.0%/yr for women age 65 to 74 years, and 1.1%/yr for women age ≥ 75 years. From 1980 to 1997, the adjusted risk of breast cancer death in newly diagnosed patients decreased by 3.6%/yr for women age less than 75 years versus 1.3%/yr for women age ≥ 75 years ($P < .001$). Over this time interval, the 10-year absolute risk of breast cancer death decreased by 15.3% for women age 50 to 64 years (from 31.9% to 16.6%) but by only 7.5% (from 24.8% to 17.4%) for women age ≥ 75 years.

Conclusion
Breast cancer outcomes have preferentially improved in women age less than 75 years. Focused research is needed to improve outcomes in older women.

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INTRODUCTION

Breast cancer afflicts women across a wide age range; approximately 25% of cases occur in women less than age 50 years, and 20% of cases occur in women greater than age 75 years. The natural history and outcomes of breast cancer have been observed to vary by age. Breast cancers diagnosed in younger women are thought to be more biologically aggressive and are more likely to be caused by an underlying heritable breast cancer syndrome.[1-5] Thus, both locoregional and systemic therapies tend to be more aggressive for younger women. In contrast, breast cancers diagnosed in older women are thought to be more biologically indolent, and there is a higher prevalence of comorbid illness in this population.[6-11] Therefore, therapy tends to be less aggressive for older women.

Recent data demonstrated that breast cancer death rates in the US population have declined during the past decade as a result of improvements in early detection and treatment.[12,13] However, despite the known variations in both breast cancer biology and treatment by age, it is not known whether the decrease in breast cancer death rates has been experienced broadly by women of all ages or selectively by women only in certain age groups. The identification of age groups that have not experienced commensurate improvements in breast cancer outcomes is critically important to identify subpopulations in need of targeted research. Accordingly, we examined the change over

time for two outcomes, the rate of breast cancer death in the general population and the risk of breast cancer death in newly diagnosed patients, and we compared the change over time in these outcomes across the age spectrum. Because recent research indicated a growing disparity in outcomes for black compared with white patients,[14-17] we quantified race-based trends in outcomes as well to provide an immediate context for our results.

The rate of breast cancer death in the general population and the risk of breast cancer death in newly diagnosed patients are complementary outcome measures that provide a relatively complete perspective on trends in breast cancer outcomes. Breast cancer death rates are typically expressed as the number of breast cancer deaths per 100,000 individuals, are inclusive of the entire US population, are available through recent years, and are not sensitive to length or lead time bias, but they are limited because variables such as the stage or age at diagnosis are not available. The risk of breast cancer death refers to the probability that a patient diagnosed with breast cancer will die from breast cancer within a certain timeframe. The risk of breast cancer death is directly clinically applicable to individual patients and can be adjusted for variables such as age or stage at diagnosis but is limited in that it is subject to a length or lead time bias and, by definition, cannot be assessed for the most current diagnosis years because sufficient follow-up is required to measure survival over time.

METHODS

Rate of Breast Cancer Death

We characterized time trends in breast cancer death rates by age and race for the US population by using cause-of-death data abstracted from death certificates compiled in National Vital Statistics Reports from 1980 to 2007.[18] This data source categorizes age into the following four age groups that are used throughout this article: 20 to 49, 50 to 64, 65 to 74, and ≥ 75 years. The yearly change in breast cancer death rates by age and race category was estimated by using linear regression for the years 1990 through 2007. This range of years was selected on the basis of a visual inspection of death-rate curves that suggested that an inflection point occurred beginning in approximately 1990. A sensitivity analysis was conducted to determine whether changing the range of years to from 1993 to 2007 would impact results.

Risk of breast cancer death. Time trends in the cumulative incidence of breast cancer death were calculated by using the cumulative incidence method[19] with data abstracted from the Surveillance, Epidemiology, and End Results (SEER) nine-registry cohort (SEER-9), which accounted for approximately 10% of the US population. This cohort was initially created in the mid-1970s and tracked data on incident cancer cases and causes of death abstracted from death certificates through 2007. Although the reliability of death-certificate data has been questioned, recent analyses of SEER data suggested a high level of accuracy in cause-of-death coding for common cancers. For example, a study that used the SEER-9 cohort compared the estimates of 5-year relative survival with cause-specific survival (as determined from death-certificate data) and revealed that breast cancer relative-survival estimates were slightly higher than breast cancer–specific survival (BCSS) estimates, which suggested that the vast majority of breast cancer deaths are captured by death-certificate data.[20] The cause-of-death coding in SEER was also validated for colon cancer.[21]

From the SEER-9 cohort, we selected women with incident breast cancers diagnosed between 1980 and 1997 because this allowed for a minimum potential follow-up of 10 years for surviving patients. Ten years of follow-up is an important milestone for at least two reasons. First, the majority of breast cancer deaths (approximately 65% of women with node-negative breast cancer and 85% of women with node-positive breast cancer)[22] occur within 10 years of diagnosis. Second, 10-year BCSS is a commonly used outcome in randomized clinical trials,[23-27] and the choice of this range of diagnosis years enabled calculation of 10-year BCSS in this cohort and comparison with other studies.

From a cohort of 293,709 women age ≥ 20 years with incident breast cancers diagnosed between 1980 and 1997 in the SEER-9 registries, we chose to exclude women with only in situ cancer (n = 33,211) because in situ breast cancer is rarely thought to be life threatening. We also excluded women with nonepithelial histologies (n = 945), no pathologic confirmation (n = 4,868), and a history of prior cancer (n = 42,090), which yielded a total of 219,024 women in the analytic cohort (patients could be excluded for > one reason). Covariates included age at diagnosis, year of diagnosis, race, SEER registry, and SEER historic stage, which was defined as local (limited to the breast without evidence of spread), regional (spread beyond the breast to nearby lymph nodes or organs or tissues), distant (spread beyond the breast to distant lymph nodes or organs), or unstaged (insufficient information to determine stage).

The cumulative incidence of breast cancer death at 10 years was calculated by using the cmprsk package in R2.13.0 (R Foundation for Statistical Computing, Vienna, Austria), with nonbreast cancer death considered a competing risk.[19] Differences in the risk of breast cancer death by covariate strata were assessed by using Gray's test. Competing risk regression determined the adjusted impact of the year of diagnosis on risk of breast cancer death. Interaction terms for age by year and race by year were also tested to compute the yearly change in the risk of breast cancer death by age and race categories and to determine whether improvements in the risk of breast cancer death over time differed in a statistically significant manner across age and race strata. The cut point for age in the interaction term was selected at 75 years on the basis of results of the analysis of breast cancer death rates.

All analyses were conducted by using SAS (v9.2; SAS Institute, Cary, NC). This study was granted an exempt status by The University of Texas MD Anderson Cancer Center Institutional Review Board.

RESULTS

Rate of Breast Cancer Death

Breast cancer death rates were stable from 1980 to 1989 for women age 20 to 64 years and increased for women age ≥ 65 years (Appendix Table A1, online only; Fig 1). In approximately 1990, breast cancer death rates began to decrease. Between the years of 1990

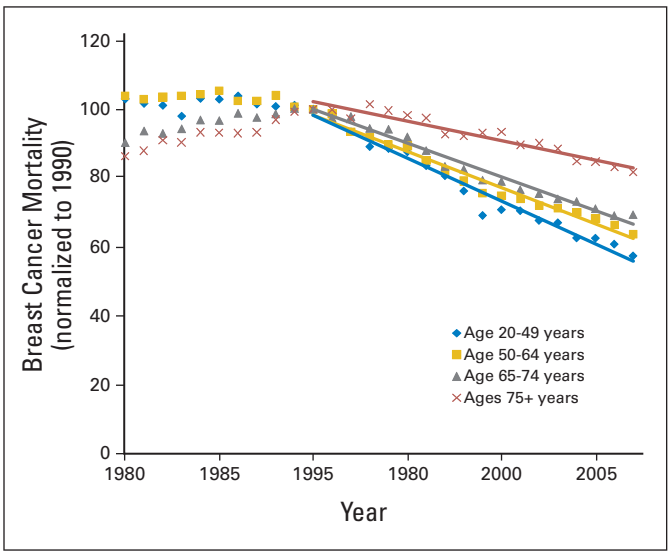

Fig 1. Breast cancer death rates for the US population from 1980 to 2007 normalized to the group specific death rate in 1990 (because this graph presents data relative to 1990, all age groups have a value of 100 for the year 1990). Solid lines represent the group-specific linear regression estimate for breast cancer death rates from 1990 to 2007.

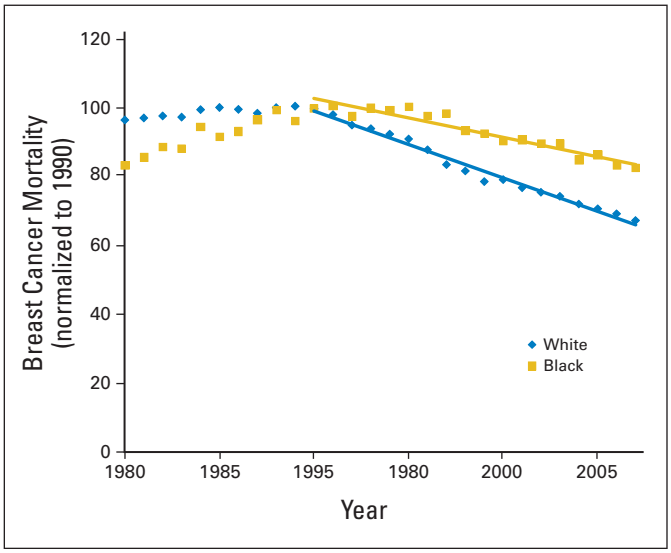

Fig 2. Breast cancer death rates for the US population from 1980 to 2007 normalized to the group-specific death rates rate in 1990 and age adjusted to the US 2000 population (because this graph presents data relative to 1990, all race groups have a value of 100 for the year 1990). Solid lines represent the group-specific linear regression estimate for breast cancer death rates from 1990 to 2007.

through 2007, the largest decrease in breast cancer death rates was noted in women age 20 to 49 years at 2.49%/yr (95% CI, 2.27% to 2.71%/yr), and the smallest decrease in breast cancer death rates was noted for women age ≥ 75 years at 1.14%/yr (95% CI, 0.97% to 1.31%/yr; the percentage rate of change was relative to the age-specific death rates in 1990; Fig 1). With regard to race, breast cancer death rates decreased by 1.96%/yr for whites (95% CI, 1.83% to 2.08%/yr) and 1.12%/yr for blacks (95% CI, 0.94% to 1.31%/yr; Fig 2).

The yearly percentage decrease in breast cancer death rates from 1990 to 2007 by age and race is listed in Figure 3, which illustrates that

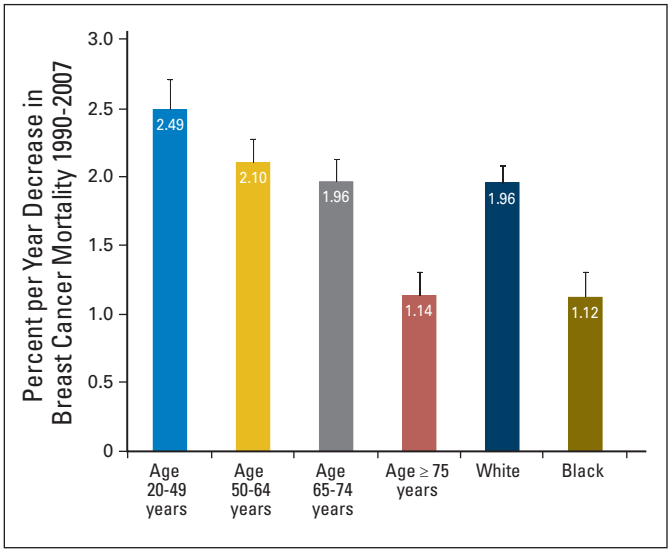

Fig 3. Yearly decrease in breast cancer death rates for the US population was calculated by using linear regression conducted on group-specific breast cancer death rates data normalized to group-specific death rates in 1990. Error bars represent upper bounds of 95% CIs.

Table 1. Baseline Patient Demographics and Characteristics and Cumulative Incidence of Breast Cancer Death for the SEER-9 Cohort Diagnosed Between 1980 and 1997

Demographic or Characteristic	No. of Patients	%	10-Year Cumulative Incidence of Breast Cancer Death (%)	*P**
Age at diagnosis, years				
20-49	53,438	24	25.3	< .001
50-64	70,135	32	23.2	
65-74	51,797	24	20.5	
≥ 75	43,654	20	20.1	
Year of diagnosis				
1980-1984	47,948	22	29.6	< .001
1985-1989	60,713	28	23.4	
1990-1994	66,723	30	19.5	
1995-1997	43,640	20	17.7	
Race/origin				
White	182,927	84	21.5	< .001
Black	16,979	8	33.4	
Asian/Pacific Islander	10,373	5	18.8	
Hispanic	7566	3	24.8	
Other/unknown	1179	1	21.4	
SEER registry				
San Francisco	36,888	17	21.0	< .001
Connecticut	36,250	17	22.2	
Metropolitan Detroit	38,660	18	25.7	
Hawaii	8455	4	18.3	
Iowa	28,823	13	22.6	
New Mexico	11,141	5	23.7	
Seattle (Puget Sound)	30,906	14	20.2	
Utah	10,600	5	22.1	
Metropolitan Atlanta	17,301	8	24.0	
SEER historic stage				
Local	127,218	58	9.9	< .001
Regional	72,787	33	33.5	
Distant	13,015	6	76.2	
Unknown	6004	3	37.4	

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; SEER-9, SEER nine registries.
*Calculated by using Gray's test.

the demographic groups with the smallest decline in death rates were women age ≥ 75 years and blacks. Results for both the age and race death-rate trends were similar in a sensitivity analysis that normalized death rates to the year 1993 rather than to 1990.

Risk of Breast Cancer Death

For the 219,024 women in this cohort who were diagnosed with breast cancer between 1980 and 1997, 58.9% of women were followed until death while those alive at last contact had a median follow-up of 15.3 years (Table 1). The risk of breast cancer death within 10 years of diagnosis decreased from 29.6% for women diagnosed in 1980 to 1984 to 20.1% for women diagnosed from 1995 to 1997 ($P < .001$). Age at diagnosis, race, SEER registry, and SEER historic stage were also associated with the risk of breast cancer death (Table 1).

In multivariate analysis, the risk of breast cancer death decreased by a relative amount of 4.5% per diagnosis year (95% CI, 4.3% to 4.7%) after adjusting for age, race, and SEER registry (Table 2). Because some of this improvement may have been attributed to stage migration associated with increased use of screening, we created a

Table 2. Predictors of Risk of Breast Cancer Death in Competing-Risks Regression

Predictor	Without Stage Adjustment			With Stage Adjustment		
	HR	95% CI	*P*	HR	95% CI	*P*
Age at diagnosis, years*						
20-49	1			1		
50-64	0.912	0.893 to 0.931	< .001	0.926	0.906 to 0.946	< .001
65-74	0.791	0.773 to 0.810	< .001	0.830	0.809 to 0.850	< .001
≥ 75	0.718	0.700 to 0.737	< .001	0.732	0.712 to 0.753	< .001
Year of diagnosis*						
Continuous variable	0.955	0.953 to 0.957	< .001	0.967	0.966 to 0.969	< .001
Race*						
White				1		
Black	1.571	1.527 to 1.616	< .001	1.379	1.337 to 1.422	< .001
Other/unknown	1.067	1.031 to 1.104	< .001	1.011	0.976 to 1.048	0.54
SEER registry*						
San Francisco	1			1		
Connecticut	1.097	1.065 to 1.129	< .001	1.015	0.985 to 1.046	0.34
Metropolitan Detroit	1.183	1.151 to 1.216	< .001	1.101	1.069 to 1.113	< .001
Hawaii	0.879	0.833 to 0.927	< .001	0.923	0.874 to 0.975	0.004
Iowa	1.149	1.114 to 1.185	< .001	1.108	1.073 to 1.144	< .001
New Mexico	1.194	1.147 to 1.244	< .001	1.121	1.074 to 1.170	< .001
Seattle (Puget Sound)	1.018	0.987 to 1.050	0.25	1.013	0.981 to 1.045	0.43
Utah	1.122	1.076 to 1.171	< .001	1.113	1.064 to 1.163	< .001
Metropolitan Atlanta	1.080	1.043 to 1.119	< .001	1.068	1.029 to 1.109	< .001
SEER historic stage*						
Local				1		
Regional				3.325	3.263 to 3.389	< .001
Distant				13.657	12.267 to 14.060	< .001
Unknown				3.921	3.759 to 4.089	< .001
Interaction term†						
Age ≥ 75 years by year	1.019	1.014 to 1.024	< .001	1.025	1.019 to 1.030	< .001
Race by year	1.025	1.019 to 1.030	< .001	1.022	1.016 to 1.028	< .001

NOTE: HRs presented in this model represent an average for the entire study interval inclusive of diagnosis years 1980-1997.
Abbreviations: HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results.
*Parameter estimates are from models without interaction terms.
†For the interaction term of age by year, the age at diagnosis was entered into the model as a dichotomous variable with a cut point at age 75 years. For the interaction term of race by year, patients with other/unknown race (n = 1,179) were excluded from the model.

second model that also included adjustment for the SEER historic stage, which crudely accounted for changes in stage over time. With stage adjustment, the risk of breast cancer death still decreased by 3.3% per diagnosis year (95% CI, 3.1% to 3.4%; Table 2). The addition of an interaction term of age ≥ 75 years with year in the fully adjusted model indicated that risk of breast cancer death decreased more dramatically for younger women than older women ($P < .001$), with a decrease of 3.6%/yr (95% CI, 3.4% to 3.8%/yr) for women age less than 75 years compared with 1.3%/yr (95% CI, 0.8% to 1.7%/yr) for women age ≥ 75 years. Similarly, the addition of an interaction term of race with year indicated that risk of breast cancer death decreased more substantially for white women than black women ($P < .001$), with an improvement of 3.6%/yr (95% CI, 3.4% to 3.7%/yr) for white women compared with 1.4%/yr (95% CI, 0.9% to 2.0%/yr) for black women.

Regarding absolute risks, from 1980 to 1997, the 10-year absolute risk of breast cancer death decreased by 10.1% for women age 20 to 49 years at diagnosis, 15.3% for women age 50 to 64 years, 12.5% for women age 65 to 74 years, and 7.5% for women age ≥ 75 years (Fig 4A). In 1980 to 1984, women age ≥ 75 years experienced the lowest risk of 10-year breast cancer death at 24.8% compared with risks of 28.0% for women age 65 to 74 years, 31.9% for women age 50 to 64 years, and 31.6% for women age 20 to 49 years. However, by 1995 to 1997, women age ≥ 75 years experienced a higher risk of breast cancer death than other postmenopausal women, with a risk of 17.3% for women age ≥ 75 years compared with risks of 15.4% for women age 65 to 74 years and 16.6% for women age 50 to 64 years (Fig 4B; Appendix Fig A1, online only). These findings persisted for each stage category (Appendix Fig A2, online only). There was also a similar, although less dramatic, difference by race, whereby the 10-year risk of breast cancer death decreased by 10.2% for blacks and 12.3% for whites (Appendix Figs A3 and A4, online only).

DISCUSSION

Our analysis revealed that both the rate of breast cancer death in the general population and the risk of breast cancer death in newly diagnosed patients decreased two to three times more rapidly for younger women compared with older women age ≥ 75 years. As a result, although women age ≥ 75 years experienced the lowest risk of breast cancer death among patients diagnosed in 1980 to 1984, by 1995 to 1997, women age ≥ 75 years experienced a higher risk of

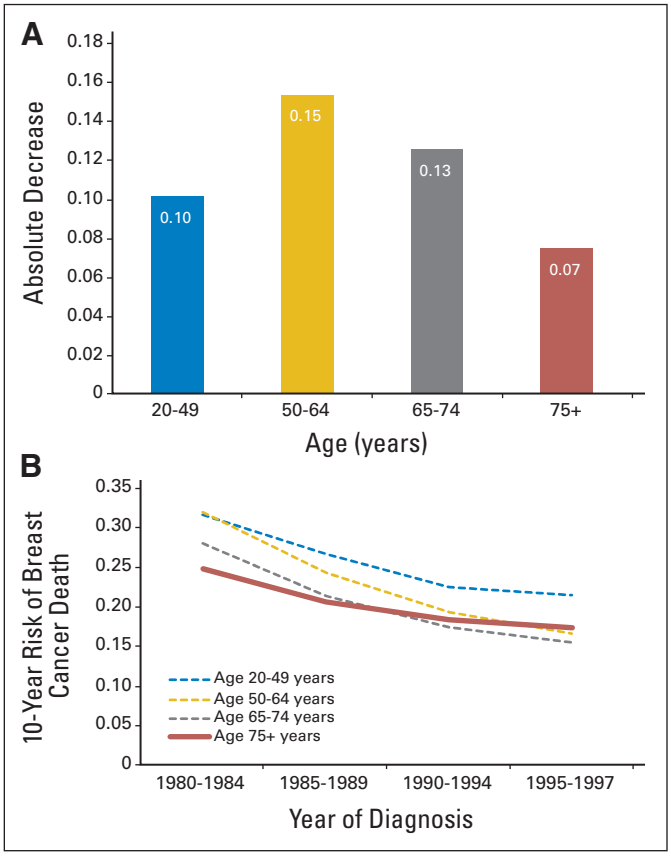

Fig 4. (A) Vertical bars represent the absolute decrease in 10-year risk of breast cancer death calculated via the cumulative incidence method for patients diagnosed in 1995 to 1997 compared with patients diagnosed in 1980 to 1984. (B) Ten-year risk of breast cancer death is plotted for patients diagnosed in 1980 to 1984, 1985 to 1989, 1990 to 1994, and 1995 to 1997 for each age group. In 1980 to 1984, women age ≥ 75 years experienced the lowest risk of breast cancer death, but by 1995 to 1997, women age ≥ 75 years experienced a higher risk of breast cancer death than women age 50 to 64 and 65 to 74 years.

breast cancer death than women between the age 50 to 74 years, which suggested that older women may have missed out on advances in breast cancer diagnosis and treatment. Notably, approximately 40,000 women age ≥ 75 years are diagnosed with breast cancer each year in the United States, which is a number that is comparable with the yearly incidence in all age groups combined for common malignancies such as pancreatic or rectal cancer.[28] Furthermore, older women are the most rapidly growing cohort of patients with breast cancer, with 57% growth expected over the next 20 years as the US population ages.[29]

Recent epidemiologic studies have highlighted dramatic improvements in breast cancer outcomes that have been attributed to improvements in both screening and treatment. For example, Berry et al[12] created a consortium of seven independent teams of biostatisticians, which ultimately concluded that improvements in screening and treatment contributed approximately equally to the observed decline in breast cancer death rates in the United States. In contrast, a longitudinal, population-based study from Norway conducted in women age 50 to 69 years concluded that improvements in treatment accounted for approximately two-thirds of the observed death rate reduction over time, with screening playing a less significant role.[13] Specific improvements in treatment that are thought to have contributed to improved outcomes include the development and dissemination of systemic chemotherapy and endocrine therapy, targeted therapies such as trastuzumab, and improvements in radiation-therapy delivery.

Although our data provided reassurance that younger women have experienced substantial gains in breast cancer outcomes as a result of improvements in screening and treatment, these gains do not appear to have fully extended to the oldest 20% of patients with breast cancer. There are several underlying factors that may have accounted for this finding. With regard to screening, recent data indicated that the use of screening mammography is lowest for older women,[30] and in addition, the US Preventative Task Force currently does not recommend screening mammography for women greater than age 74 years. With regard to treatment, until recently, knowledge regarding the optimal treatment for older women has been limited, because older women have been underrepresented, if not excluded entirely, from many breast cancer clinical trials.[31-33] Second, there has been conflicting evidence regarding the magnitude of the benefit of adjuvant chemotherapy by age. The data from the Early Breast Cancer Trialists' Collaborative Group demonstrated a decreasing benefit from adjuvant chemotherapy by age; however, few women greater than age 70 years were included in these clinical trials, and there was limited power to measure a benefit of chemotherapy in this subpopulation.[34] Nevertheless, this uncertainty regarding the magnitude of benefit of chemotherapy for older women with breast cancer may have contributed to its relative underuse in this patient population.[35,36] Third, because older adults are known to experience an increased risk of chemotherapy toxicity,[37,38] the dose intensity is often reduced in this patient population,[39] which further compromises treatment effectiveness. Other components of adjuvant treatment may also be compromised in the older adult, including the receipt of radiation therapy[40] and compliance with endocrine therapy.[41-45] Together, the lower prescription of adjuvant therapy, or inability to deliver the therapy at recommended doses, may contribute to smaller declines in breast cancer death rates in older adults.

In recent years, data regarding adjuvant systemic therapy for older women have started to emerge. For example, a randomized clinical trial demonstrated that standard adjuvant polychemotherapy decreased the risk of relapse and death rates in older adults with breast cancer compared with single agent capecitabine.[46] Retrospective data from cooperative group studies further corroborated that older adults derived similar benefits from adjuvant chemotherapy as did younger adults.[47] Together, these studies supported a prescription of therapy on the basis of tumor biology rather than age. However, studies to date have demonstrated that increasing age is a risk factor for decreasing adjuvant chemotherapy dose intensity, which may compromise effectiveness. Lyman et al[39] evaluated the incidence and predictors of low-dose intensity in 19,898 community-based patients with early stage breast cancer and demonstrated that patients age ≥ 65 years were at risk for a reduced relative dose intensity with 66.5% of patients having received a relative dose intensity of less than 85%. Therefore, research is needed to identify those older adults at risk for reduced dose intensity and to develop tolerable but effective chemotherapeutic regimens for this patient population.

In addition to older women, our findings suggested that black women are another sociodemographic group that has not fully reaped benefits of improved breast cancer outcomes. The race-based gap in outcomes emerged in the early 1980s and continues to increase. For example, in 2006, the absolute rate of breast cancer death rate was 38%

higher in blacks than whites.[17,48] Although estrogen receptor (ER)–negative breast cancers, which are generally thought to be more lethal, are more common in black than white patients, recent data indicated that blacks experience a higher risk of breast cancer death than did whites irrespective of ER status. In contrast, generally less lethal ER-positive breast cancers are more common in older than younger women,[11] but outcomes have still improved more rapidly in younger women who have a larger proportion of ER-negative and biologically aggressive cancers, which suggests that the failure of breast cancer outcomes to improve dramatically in older women may be due primarily to suboptimal screening and/or treatment rather than tumor biology.

This study provided a nationally representative perspective on trends in breast cancer outcomes and was strengthened by using two complementary outcome measures from different data sources that yielded similar findings. Nevertheless, certain key variables such as ER status, tumor size, and nodal status were not available because they were not reliably coded until the early to mid-1990s. However, because older women are more likely than younger women to have tumors with favorable biologic features,[26] adjustment for covariates such as ER status could have actually further accentuated the measured disparity in the improvement of breast cancer outcomes for older women. In addition, we assumed that breast cancer deaths were reported with equal accuracy across the age spectrum. If breast cancer as a cause of death were coded more accurately for one age group than another, this could either have accentuated or mitigated the measured difference in outcomes by age depending on the direction of the association.

In summary, we reported an evolving disparity in breast cancer outcomes by age, with gains in outcomes for younger women outpacing those for older women. Research is needed to understand preferences of older adults for screening and treatment and to identify optimal adjuvant-therapy regimens that are both effective and tolerable in the setting of the functional status, comorbid illnesses, and social support of older women.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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