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EPIDEMIOLOGY

Quantifying the relationship between age at diagnosis and breast cancer-specific mortality

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Abstract

Purpose The relationship between age at diagnosis and breast cancer-specific mortality (BCSM) is unclear. The aim of this study was to examine the nature of this relationship using rigorous statistical methodology.

Methods A historical cohort study of adult women with invasive breast cancer in the SEER database from 2000 to 2015 was conducted. Multivariable Cox's cause-specific hazards model was used to evaluate the association of age at diagnosis with risk of BCSM. Functional relationship of age was assessed using cumulative sums of Martingale residuals and the Kolmogorov-type supremum test.

Results A total of 206,332 women were eligible for study. Mean age at diagnosis was 59.7 ± 13.8 years. Median follow-up was 80 months. During the study period, 21,771 women (10.6%) died from breast cancer and 18,566 (9.0%) died from other causes. Cumulative incidence of BCSM at 120 months post-diagnosis was 14.4% (95% CI 14.2–14.6%). Age was found to be quadratically related to the risk of BCSM ($p < 0.001$), with a nadir at 45 years of age. The final Cox model suggests that a 30-year-old woman has approximately the same adjusted BCSM risk (HR 1.187, 95% CI 1.187–1.188) as a 60-year-old woman (HR 1.174, 95% CI 1.174–1.175).

Conclusions Women diagnosed with breast cancer at the extremes of age suffer disproportionate rates of cancer-specific mortality. The relationship between age at diagnosis and adjusted risk of BCSM is complex, consistent with a quadratic function. With the growing appreciation for breast cancer as a heterogeneous disease, it is essential to accurately address age as a prognostic risk factor in predictive models.

Keywords Breast cancer · Mortality · Differential mortality · Age groups · Age distribution · Statistical model

Abbreviations

AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
BCSM	Breast cancer-specific mortality
CI	Confidence interval
SD	Standard deviation
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor
HR	Hazard ratio
PR	Progesterone receptor
SEER	Surveillance, epidemiology, and end results

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Introduction

Over the past several decades, survival of women with breast cancer has increased in most developed nations, with adjusted 5-year survival rates of at least 80% in over thirty countries in the late 2000s [1]. In the United States, age-standardized death rates for breast cancer have decreased since 1975 [2], partly due to the initiation of screening mammography and advances in adjuvant therapies [3]. However, these longitudinal improvements in survival have not been observed uniformly for all women with breast cancer; the magnitude is greatest among non-Hispanic white women residing in certain geographic regions [2]. Given the

heterogeneity of breast cancer, it is plausible that there are other factors contributing to survival disparities.

Although age is a recognized risk factor for the development of breast cancer [4–6], the relationship between age at diagnosis and mortality from breast cancer is less clear. Disproportionately higher rates of breast cancer-specific mortality (BCSM) have been observed in separate cohorts among younger [7–12] as well as older [11–16] women, but age thresholds were inconsistent. These studies, like many breast cancer outcome analyses, included age as a categorical or binomial variable in multivariable models. When a continuous variable such as age is found to violate model assumptions, it may be statistically sound to convert it to a categorical variable; however, this approach may not be biologically valid. Additionally, categorization of patients into biologically arbitrary groups such as decades or quartiles risks loss of granularity and decreased statistical power to detect small but meaningful differences.

The aim of our study was to examine the functional relationship between age at diagnosis and risk of BCSM using statistical methods that maintain the age continuum and thus enable determination of accurate biological inflection points.

Methods

Data source and study population

Data were extracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. SEER collects cancer incidence and survival data from multiple registries that cumulatively cover approximately 34.6% of the United States population [17].

SEER*Stat [18] was used to identify adult (≥ 18 years old) females with only one malignant primary tumor in the database diagnosed with breast cancer between January 1, 2000 and December 31, 2015. Demographic variables collected included: age at diagnosis, race, year of diagnosis, vital status, and cause of death. Autopsy-only cases and cases with incomplete or unknown survival data were excluded from the analysis. Clinical prognostic risk factors collected included: tumor grade, adjusted American Joint Commission on Cancer (AJCC) 6th edition stage (years of diagnosis 2000–2010), derived AJCC 7th edition stage (years of diagnosis 2010–2015), estrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor (HER2) status. Per accepted standards, borderline ER and PR values were recoded as positive and borderline HER2 values were recoded as unknown [19]. As SEER did not require recording of HER2 data until 2010, a subgroup analysis of women diagnosed with breast cancer from January 1, 2010–December 31, 2015 was also performed.

Statistical analysis

Continuous variables are summarized by presenting the number of non-missing observations, mean, standard deviation (SD), median, and interquartile range while categorical variables are summarized by presenting the number of patients and percentage for each category.

Median follow-up was calculated using the reverse Kaplan–Meier method. Cumulative incidence function for BCSM was estimated with death from other causes included as a competing event. Patients alive at the time of last follow-up and/or at the end of the study period were right censored.

Multivariable Cox's cause-specific hazards models were used to evaluate the association of age at diagnosis with risk of BCSM while controlling for clinical prognostic risk factors. Hazard ratios (HRs) and 95% confidence intervals (CIs) are provided as measures of strength of association and precision, respectively. The functional form of age at diagnosis on the risk of BCSM was assessed using cumulative sums of Martingale residuals [20] and the Kolmogorov-type supremum test based on a sample of 1000 simulated residual patterns. Additional models were fit to the data with age at diagnosis included as a categorical variable with indicators variables based on age quartiles and age deciles as well as a continuous variable using the natural logarithmic transformation. Choice of final model was based on the Akaike information criterion (AIC).

The effect of age at diagnosis on the risk of BCSM was further assessed in the final model by including age as time-dependent covariate in the Cox model. This was done by dichotomizing the survival time variable before forming the product with age in the Cox model. Specifically, we evaluated whether the effect of age was more pronounced early versus late post-diagnosis of breast cancer.

Analyses were performed using SAS version 9.4 statistical software (Cary, NC). All tests of statistical significance were two-sided, and significance was defined as a p value of less than 0.05.

Results

Description of population

A total of 206,332 women were included in the analysis. Demographic and clinical characteristics are summarized in Table 1. The mean age at diagnosis was 59.7 (SD 13.8).

The median follow-up was 80 months (interquartile range 37–132 months). Overall, 40,337 women (19.5%) were deceased, of which 21,771 (10.6% of the

Table 1 Demographic and clinical characteristics of the total population of 206,332 women

Variable	Statistic or category	Number (%)
Age at diagnosis (years)	Mean, standard deviation	59.7, 13.8
	Median, interquartile range	59, 49–70
Race	White	163,062 (79.0)
	Black	21,218 (10.3)
	Other/unknown	22,052 (10.7)
Grade	I	46,640 (22.6)
	II	87,356 (42.3)
	III	70,973 (34.4)
	IV	1363 (0.7)
ER status	Negative	38,481 (18.7)
	Positive	160,797 (77.9)
	Unknown	7054 (3.4)
PR status	Negative	59,280 (28.7)
	Positive	139,513 (67.6)
	Unknown	7539 (3.7)
HER2 status	Before 2010	116,962 (56.7)
	2010+:negative	72,489 (35.1)
	2010+:positive	13,181 (6.4)
	2010+:unknown	3700 (1.8)
Subtype	Before 2010	116,962 (56.7)
	2010+:HR+/HER2+	9216 (4.5)
	2010+:HR−/HER2+	3945 (1.9)
	2010+:HR+/HER2−	62,833 (30.5)
	2010+:triple negative	9580 (4.6)
	2010+:unknown	3796 (1.8)
T stage	T1	123,899 (60.1)
	T2	59,300 (28.7)
	T3	11,153 (5.4)
	T4	6829 (3.3)
	Unknown	5151 (2.5)
N stage	N0	136,170 (66.0)
	N1	48,543 (23.5)
	N2	12,473 (6.1)
	N3	7699 (3.7)
	Unknown	1447 (0.7)
Overall stage	I	101,999 (49.4)
	II	70,955 (34.4)
	III	24,887 (12.1)
	IV	8491 (4.1)

ER estrogen receptor, *PR* progesterone receptor, *HR* hormone receptor, *HER2* human epidermal growth factor receptor

total population) died of breast cancer. The unadjusted cumulative incidence of BCSM at 5 years was 9.7% (95% CI 9.6–9.9%) and at 10 years was 14.4% (95% CI 14.2–14.6%).

Multivariable analysis of BCSM

Observed cumulative Martingale residual plot against age along with 20 simulated realizations under the assumption of linearity is presented in Fig. 1. The plot suggests a more elaborate functional form of age is warranted (supremum test: $p < 0.001$). The sigmoidal shape indicates that the functional relationship of age with risk of BCSM may be better captured using a quadratic term for age. When fitting this model, the observed cumulative Martingale residual process was more typical of the simulated realizations. Results of the final multivariable model, selected by AIC (Fig. 2), are provided in Table 2.

The vertex of the quadratic function (Fig. 3) occurs at approximately 45 years of age, which suggests that adjusted risk of BCSM decreases from 18 to 45 years (HR per-year increase = 0.972; 95% CI 0.968–0.977) and then increases thereafter (HR per-year increase = 1.031; 95% CI 1.030–1.032). A 30-year-old woman has approximately the same adjusted BCSM risk (HR 1.187, 95% CI 1.187–1.188) as a 60-year-old woman (HR 1.174, 95% CI 1.174–1.175).

The unadjusted risk of BCSM is relatively accentuated in younger women and attenuated in older women, with a nadir at age 56 (Fig. 4).

Age-dependent risk of BCSM also varies over time, as demonstrated in Fig. 5, which depicts the HR at various time points after diagnosis. In this figure, the HR is reported in terms of per-year increase in risk of BCSM in the first month post-diagnosis, in the first 3 months post-diagnosis, in the first 6 months post-diagnosis, and so on. The plot demonstrates that the effect of age on the adjusted risk of BCSM (HR per-year increase) varies over time, especially in women 45 years of age or less. For example, in younger women, the effect of age (per-year increase) on the risk of BCSM in the first month post-diagnosis is higher than the effect of age (per-year increase) on the risk of BCSM in the first 3 months post-diagnosis. The trend in the HR in younger women suggests the per-year effect of age on the risk of BCSM diminishes over time while for older women (age > 45 years) the effect is relatively consistent.

The final Cox model (Table 2) included both age and age^2 as covariates to accurately account for the quadratic relationship between age and BCSM age. The final model also included variables known to impact prognosis and year of diagnosis to control for possible changes in treatment patterns over time. All variables were found to be independent predictors of BCSM ($p < 0.0001$).

Subgroup analysis: 2010–2015

A total of 89,370 women were diagnosed from 2010 to 2015. Demographic and clinical characteristics are summarized in Table 3. The mean age at diagnosis was 60.1 (SD 13.5).

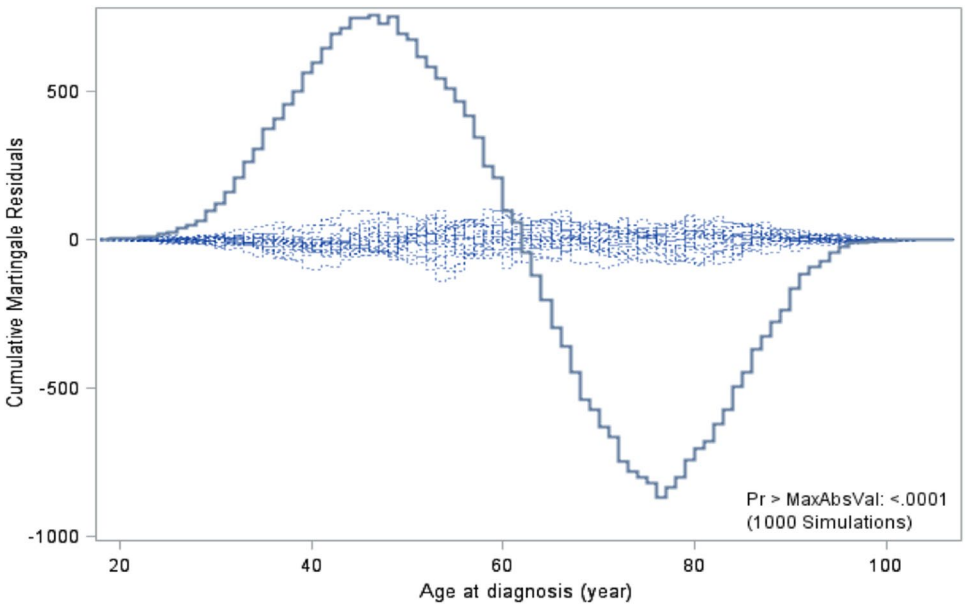

Fig. 1 Observed cumulative Martingale residual plot against age at diagnosis with 20 simulated realizations. This plot is used to determine the functional form of age on the risk of breast cancer-specific mortality

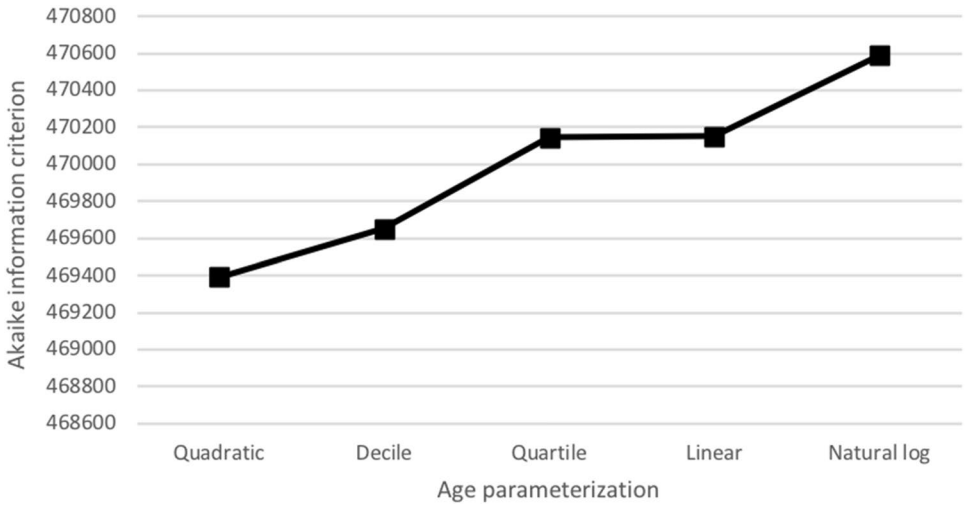

Fig. 2 Akaike information criterion (AIC) for candidate Cox models. The model with the smallest value is considered the best model

The median follow-up was 33 months (interquartile range 15–51 months). Overall, 7047 women (7.9%) were deceased, of which 4523 (5.1% of the total population) died of breast cancer. The unadjusted cumulative incidence of BCSM at 5 years was 8.6% (95% CI 8.3–8.8%). The functional form of age at diagnosis on the risk of BCSM was found to be quadratic (supremum test: $p < 0.001$, Supplementary Figs. 1, 2). All variables except year of diagnosis were found to be independent predictors of BCSM on multivariable modeling ($p < 0.0001$, Table 4).

The vertex of the quadratic function (Supplementary Fig. 3) occurs at approximately 42 years of age, which suggests that adjusted risk of BCSM decreases from 18 to 42 years (HR per-year increase = 0.964; 95% CI 0.950–0.977) and then increases thereafter (HR per-year increase = 1.037; 95% CI 1.034–1.039). A 25-year-old woman has approximately the same risk of unadjusted BCSM (HR 1.260, 95% CI 1.259–1.261) as a 60-year-old woman (HR 1.264, 95% CI 1.265–1.263). Similar trends in age-dependent adjusted risk of BCSM over time were observed (Supplementary Fig. 4).

Discussion

The relationship between age at diagnosis and BCSM is complex. We demonstrate that women at the greatest risk of mortality from breast cancer are those who are diagnosed at the extremes of age. This is the largest study to demonstrate a quadratic relationship between age at diagnosis and BCSM, and the first to report a vertex corresponding to lowest risk at age 45.

Table 2 Final multivariable Cox's cause-specific hazards models for breast cancer-specific mortality

Parameter	Comparison	*p* value	Hazard ratio (95% confidence interval)
Age	Per-year increase	< 0.0001	0.94 (0.93 to 0.94)
Age^2	Per unit increase	< 0.0001	1.00 (1.00 to 1.00)
Grade	II versus I	< 0.0001	1.74 (1.64 to 1.84)
	III versus I	< 0.0001	2.60 (2.45 to 2.76)
	IV versus I	< 0.0001	2.83 (2.51 to 3.19)
Stage	II versus I	< 0.0001	3.14 (3.00 to 3.28)
	III versus I	< 0.0001	10.36 (9.89 to 10.84)
	IV versus I	< 0.0001	51.73 (49.29 to 54.28)
Race	Black versus White	< 0.0001	1.39 (1.34 to 1.44)
	Other versus White	< 0.0001	0.87 (0.83 to 0.91)
ER status	Negative versus positive	< 0.0001	1.38 (1.32 to 1.43)
	Unknown versus positive	0.0290	1.27 (1.02 to 1.57)
PR status	Negative versus positive	< 0.0001	1.41 (1.36 to 1.46)
	Unknown versus positive	0.0551	1.23 (1.00 to 1.51)
Year of diagnosis	Per-year increase	< 0.0001	0.97 (0.97 to 0.97)

ER estrogen receptor, *PR* progesterone receptor

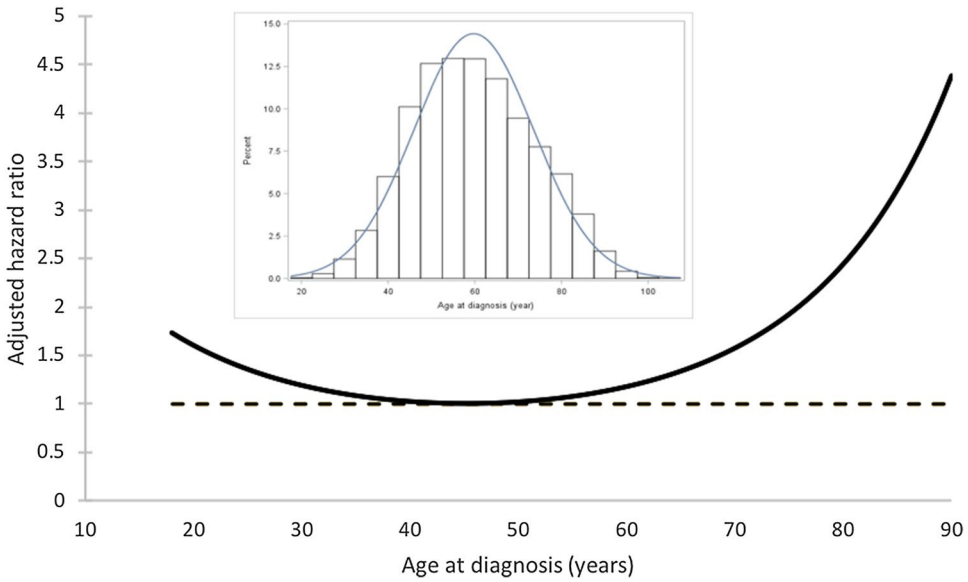

Fig. 3 The plot of the hazard ratio for increasing age based on the fit of the Cox model with age at diagnosis included as a quadratic term. The superimposed histogram demonstrates that the age distribution of is approximately normal

Two prior SEER analyses also found a quadratic relationship between age at diagnosis and BCSM, but with different vertices. Rosenberg and colleagues [21] analyzed data from 1973 to 1998 and reported a nadir in BCSM at 55 years of age. Tai and colleagues [22] found a nadir at approximately 50 years of age in a cohort of women with surgically-treated pT1–2 M0 breast cancer who were diagnosed from 1998 to 1997. In contrast, the vertex of the quadratic curve observed in our study occurred at a distinctly younger age. Possible explanations for this include differences in cohort selection criteria and inclusion of more prognostic variables such as ER status, PR status, HER2 status in our multivariable analysis—indeed, these variables are known to impact breast cancer outcomes to such a significant extent that they are now part of the AJCC prognostic staging schema [23].

Additionally, our unique observation that women in their mid-40 s are at relatively lower risk of BCSM may be partially attributable to different rates of receipt of adjuvant therapies among subsets of women. In contrast to the prior SEER analyses, women in our contemporary cohort were eligible for modern multiagent chemotherapy and endocrine therapy, which are known to improve breast cancer survival [3]. It has been demonstrated that while chemotherapy reduces mortality for many women, this may not be the case for women ≥ 80 [15]. Although younger women present with relatively higher rates of advanced disease [24] and would

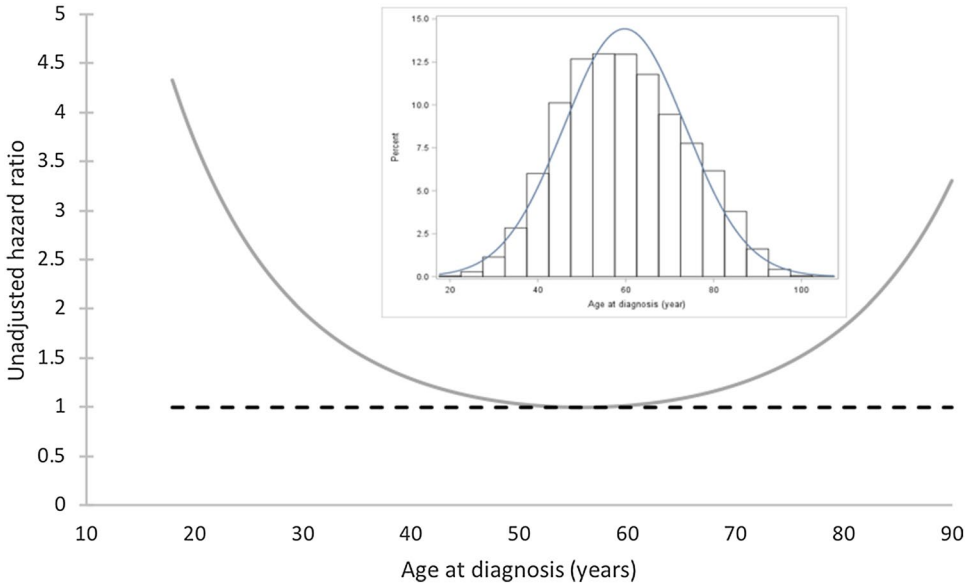

Fig. 4 Risk of breast cancer-specific mortality by age, unadjusted. The superimposed histogram demonstrates that the age distribution of is approximately normal

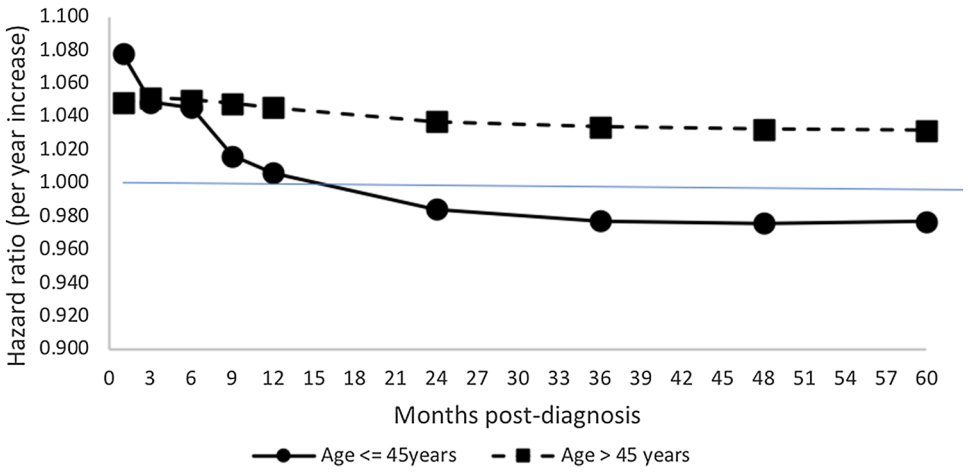

Fig. 5 Risk of breast cancer-specific mortality over time with age included as a time-dependent covariate

therefore be expected to derive more relative benefit from chemotherapy, they also have relatively higher rates of ER-negative disease [25] and thus have less to gain from endocrine therapy. While our analysis controlled for all possible prognostic risk factors, SEER does not report endocrine therapy use and has suboptimal information about chemotherapy which precludes accurate statistical analysis of the contribution of this variable to our outcome of interest [26].

Differences in tumor biology may play a significant role in our findings. Emerging evidence supports unique genetic signatures among young women with breast cancer [27, 28]. One particular presentation of breast cancer that may afflict younger women is postpartum breast cancer, which is increasingly recognized to comprise a group of biologically aggressive tumors that confer an increased risk of mortality for up to 10 years after childbirth [29]. Differences in stage and tumor subtype do not fully explain the virulence of postpartum breast cancer; it is hypothesized that postpartum parenchymal involution causes alterations in the tumor microenvironment that promote invasion and metastasis [30, 31].

The driving forces behind the breast cancer mortality disparities observed among the most elderly remain to be determined. Older women with breast cancer commonly have ER + disease, but grade and stage at diagnosis vary considerably [16, 32]. While some data support less aggressive therapy in older women with breast cancer [33–35], there is a documented pattern of undertreatment of some elderly patients, particularly with respect to chemotherapy and endocrine therapy [32, 36, 37]. Comorbidities may preclude candidacy for chemotherapy, but it is unclear why rates of endocrine therapy use among eligible elderly women are suboptimal. Many studies demonstrate an association between undertreatment and poorer survival

Table 3 Subgroup Analysis: Demographic and clinical characteristics of the 89,370 women diagnosed from 2010–2015

Variable	Statistic or category	Number (%)
Age at diagnosis (years)	Mean, standard deviation	60.1, 13.5
	Median, interquartile range	60, 50–69
Race	White	68,704 (76.9)
	Black	9888 (11.1)
	Other/Unknown	10,778 (12.1)
Grade	I	21,599 (24.2)
	II	38,676 (43.3)
	III	28,926 (32.4)
	IV	169 (0.2)
ER status	Negative	14,838 (16.6)
	Positive	73,762 (82.5)
	Unknown	770 (0.9)
PR status	Negative	24,085 (27.0)
	Positive	64,415 (72.1)
	Unknown	870 (1.0)
HER2 status	Negative	72,489 (81.1)
	Positive	13,181 (14.8)
	Unknown	3700 (4.1)
Subtype	HR+/HER2+	9216 (10.3)
	HR−/HER2+	3945 (4.4)
	HR+/HER2−	62,833 (70.3)
	Triple Negative	9580 (10.7)
	Unknown	3796 (4.3)
T stage	T1	52,760 (59.0)
	T2	27,113 (30.3)
	T3	5674 (6.4)
	T4	3419 (3.8)
	Unknown	404 (0.5)
N stage	N0	60,561 (67.8)
	N1	21,179 (23.7)
	N2	4593 (5.1)
	N3	2727 (3.1)
	Unknown	310 (0.4)
Overall stage	I	45,708 (51.1)
	II	30,083 (33.7)
	III	9602 (10.7)
	IV	3977 (4.5)

ER estrogen receptor, *PR* progesterone receptor, *HR* hormone receptor, *HER2* human epidermal growth factor receptor

outcomes [38–41], but others do not [37]. The potential confounders of frailty and undertreatment could not be controlled because SEER lacks information about comorbidities and includes limited information about treatments. In a robust analysis of SEER-Medicare data, Schonberg and colleagues found that women ≥ 80 have higher BCSM on multivariable analyses irrespective of tumor characteristics or treatment receipt [15]. There may be a subset of elderly women with breast cancer with biologically aggressive disease that has not yet been fully characterized; thus far, attempts to identify molecular signatures among the elderly have not been as fruitful as those for younger women [28, 42].

Others have observed that breast cancer mortality is age-dependent. Adami and colleagues [43] stratified women in a Swedish cohort by narrow age intervals to compare their relative survivals and found that women aged 45–49 had the most favorable prognosis. A non-linear relationship between age at diagnosis and relative survival as well as time-dependent effects of age were observed in a French cohort [44]. It is difficult to make direct comparisons between our studies, however, as Cluze and colleagues generated separate models for different tumor stages and grades, whereas we included all prognostic risk factors in a single multivariable model. Another group [45] modeled distant recurrence-free survival in cohorts from Sweden and Denmark, but did not observe a non-linear relationship between age and outcome, possibly due to differences between our outcomes of interest or the very small proportion of women < 35 years of age in the study by Forsare and colleagues.

Further studies are needed to validate these findings. If a quadratic relationship between age at diagnosis and risk of BCSM is confirmed in diverse cohorts, consideration should be given to developing a standardized way to address age when this variable is utilized in multivariable models for breast cancer outcomes. Analyses focused on other prognostic risk factors will be more robust if "nuisance variables" such as age are modeled as accurately as possible.

Breast cancer is increasingly recognized to be a heterogenous disease. The recent transition from a purely anatomic stage to one that incorporates prognostic clinical variables [23] raises the question of whether there may be additional variables which warrant inclusion in future AJCC editions. Perhaps age at diagnosis of breast cancer will prove to be a noteworthy staging criterion, as it is for differentiated thyroid cancer [46]. Of note, age is included as a prognostic variable in several validated risk assessment tools, including the two endorsed by AJCC [47, 48]. Given the observation that the effects of age on BCSM are time-dependent, the accuracy of these tools may be improved by offering multiple prognostic predictions at various time points e.g. mortality within 6 months, within 1 year, within 2 years, and so forth. More accurate predictions about prognosis can inform clinical decisions, empower patients, and ameliorate the risks of both undertreatment and overtreatment.

In conclusion, relative to women diagnosed with breast cancer in their mid-40 s, younger women and, to a greater magnitude, older women have disproportionately high rates of cancer-specific mortality. Further studies to elucidate the biological underpinnings of this observation are needed.

Table 4 Final multivariable Cox's cause-specific hazards models for breast cancer-specific mortality: Subgroup analysis (2010–2015)

Parameter	Comparison	*p* value	Hazard ratio (95% confidence interval)
Age	Per-year increase	< 0.0001	0.94 (0.93 to 0.95)
Age^2	Per unit increase	< 0.0001	1.00 (1.00 to 1.00)
Grade	II versus I	< 0.0001	1.51 (1.33 to 1.73)
	III versus I	< 0.0001	2.61 (2.29 to 2.99)
	IV versus I	< 0.0001	3.74 (2.52 to 5.53)
Stage	II versus I	< 0.0001	3.94 (3.48 to 4.46)
	III versus I	< 0.0001	15.27 (13.52 to 17.25)
	IV versus I	< 0.0001	81.67 (72.52 to 91.97)
Race	Black versus White	< 0.0001	1.26 (1.16 to 1.36)
	Other versus White	0.0001	0.81 (0.73 to 0.90)
ER status	Negative versus positive	< 0.0001	1.57 (1.45 to 1.71)
	Unknown versus positive	0.1547	1.6 (0.84 to 3.07)
PR status	Negative versus positive	< 0.0001	1.77 (1.63 to 1.92)
	Unknown versus positive	0.0633	1.8 (0.97 to 3.35)
HER2 status	Negative versus positive	< 0.0001	1.74 (1.61 to 1.89)
	Unknown versus positive	< 0.0001	1.78 (1.52 to 2.08)
Year of diagnosis	Per-year increase	0.1932	0.99 (0.96 to 1.01)

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor

Data availability The data that support the findings of this study are available from SEER but restrictions apply to the availability of these data, which were used under a signed SEER Research Data agreement for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of SEER.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent As this study is based on a publicly available database without identifying patient information, informed consent was not needed.

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