Published OnlineFirst October 17, 2018; DOI: 10.1158/1055-9965.EPI-18-0353

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Breast Cancer Mortality in Older and Younger Patients in California

Li Tao[1], Richard B. Schwab[2], Yazmin San Miguel[2], Scarlett Lin Gomez[1,3,4], Alison J. Canchola[1,3], Manuela Gago-Dominguez[2,5], Ian K. Komenaka[6], James D. Murphy[2], Alfredo A. Molinolo[2], and Maria Elena Martinez[2,7]

Abstract

Background: Breast cancer in younger patients is reported to be more aggressive and associated with lower survival; however, factors associated with age-specific mortality differences have not been adequately assessed.

Methods: We used data from the population-based California Cancer Registry for 38,509 younger (18–49 years) and 121,573 older (50 years and older) women diagnosed with stage I to III breast cancer, 2005–2014. Multivariable Cox regression models were used to estimate breast cancer–specific mortality rate ratios (MRR) and 95% confidence intervals (CI), stratified by tumor subtype, guideline treatment, and care at an NCI-designated cancer center (NCICC).

Results: Older breast cancer patients at diagnosis experienced 17% higher disease-specific mortality than younger patients, after multivariable adjustment (MRR = 1.17; 95% CI, 1.11–1.23). Higher MRRs (95% CI) were observed for older versus younger patients with hormone receptor (HR)$^+$/HER2$^-$ (1.24; 1.14–1.35) and HR$^+$/HER2$^+$ (1.38; 1.17–1.62), but not for HR$^-$/HER2$^+$ (HR = 0.94; 0.79–1.12) nor triple-negative breast cancers (1.01; 0.92–1.11). The higher mortality in older versus younger patients was diminished among patients who received guideline-concordant treatment (MRR = 1.06; 95% CI, 0.99–1.14) and reversed among those seen at an NCICC (MRR = 0.86; 95% CI, 0.73–1.01).

Conclusions: Although younger women tend to be diagnosed with more aggressive breast cancers, adjusting for these aggressive features results in older patients having higher mortality than younger patients, with variations by age, tumor subtype, receipt of guideline treatment, and being cared for at an NCICC.

Impact: Higher breast cancer mortality in older compared with younger women could partly be addressed by ensuring optimal treatment and comprehensive patient-centered care.

Introduction

Breast cancer is the most common cancer among women worldwide, accounting for a fifth of overall cancer mortality (1). In the United States, less than 20% of all breast cancer cases occur before the age of 50 years (2). Results of some studies have shown that younger compared with older breast cancer patients have poorer survival, with studies focusing on age groups less than 40 years (3–5). For breast cancer mortality endpoints, two studies based on the Surveillance, Epidemiology, and End Results (SEER) Program reported that younger compared with older breast cancer patients had higher breast cancer mortality, with HRs of 1.095 [95% confidence interval (CI), 1.101–1.183] comparing patients less than 35 with those 50 to 55 years of age in one study (6) and 1.39 (CI, 1.34 to 1.45) in the second study comparing women <40 with those 40+ years of age (7). Variations in estimates of risk could be due to the inconsistent use of referent and comparison age groups and to covariates included in multivariate models. Proposed reasons for higher mortality in younger versus older patients include later stage disease, more aggressive tumors, and less favorable tumor receptor status in younger than older patients (5, 6). However, biological, undertreatment, and socioeconomic status (SES) factors may potentially result in higher mortality among older compared with younger patients (8–11).

To our knowledge, there are no published reports regarding differences in breast cancer mortality for the age cut off of 50 years, a marker for menopausal status and for recommended initiation of screening mammography (12, 13). Furthermore, although breast cancer survival has been shown to vary according to tumor subtype (14), comparison of prognostic factors between younger and older patients by tumor subtype is poorly understood, especially in population-based settings.

Using data from the population-based California Cancer Registry (CCR), our study takes advantage of the completeness of tumor subtype information in the registry in the mid-2000s to assess breast cancer mortality differences between breast cancer patients who were younger (age 18–49) and older (age 50 and above) at diagnosis. We further assessed the moderating effects of tumor biology and clinical factors by examining whether

[1]Greater Bay Area Cancer Registry, Cancer Prevention Institute of California, Fremont, California. [2]Moores Cancer Center, University of California, San Diego, La Jolla, California. [3]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, California. [4]Department of Epidemiology and Biostatistics, University of California, San Francisco, California. [5]Fundación Galega Medicina Genómica, Instituto de Investigación Sanitaria de Santiago IDIS, Santiago de Compostela, Spain. [6]Maricopa Medical Center, Phoenix, Arizona. [7]Family Medicine and Public Health, University of California, San Diego, La Jolla, California..

Corresponding Author: Maria Elena Martinez, University of California, San Diego, 3855 Health Sciences Drive, #0901, Room 3065, La Jolla, CA 92093-0901. Phone: 858-822-3638; Fax: 858-822-2399; E-mail: e8martinez@ucsd.edu

doi: 10.1158/1055-9965.EPI-18-0353

Published OnlineFirst October 17, 2018; DOI: 10.1158/1055-9965.EPI-18-0353

mortality differences vary by tumor subtype, receiving guideline-appropriate care, and receiving care at an NCI-Designated Cancer Center (NCICC).

Materials and Methods

Study population

We obtained from CCR information about all female California residents age 18 years and older at diagnosis who were diagnosed with a first, primary invasive breast cancer [International Classification of Disease for Oncology, 3rd Edition, (ICD-O-3) site codes C50.0–50.9] during January 1, 2005, through December 31, 2014 ($n = 196,628$). As the criteria for guideline treatment were limited to patients diagnosed with American Joint Committee on Cancer (AJCC) stage I to III breast cancer, our analysis did not include patients with stage unknown or stage IV breast cancer ($n = 19,842$). Patients were additionally excluded from analysis hierarchically as follows: diagnosis by death certificate or autopsy only ($n = 19$) or diagnosis not microscopically confirmed ($n = 187$); ICD-O-3 histologic type other than 8000, 8001, 8010, 8020, 8022, 8050, 8140, 8201, 8211, 8230, 8255, 8260, 8401, 8453, 8480, 8481, 8500–8525, or 8575 ($n = 2,217$); tumor size missing because unknown ($n = 667$), no tumor noted ($n = 236$), microscopic ($n = 2,009$), diffuse ($n = 280$), or mammographic diagnosis only ($n = 54$); young patient insured by Medicare ($n = 403$); no follow-up ($n = 210$); second primary breast tumor diagnosed within 60 days of initial tumor ($n = 5,068$); bilateral tumors at initial diagnosis ($n = 7$); residential address that was uncertain or not geocodable ($n = 5,347$). Analyses thereby included 160,082 patients, of which 38,509 were younger (age 18–49) and 121,573 were older (age 50 and above, up to age 103) patients.

We obtained information from the CCR, which is derived from the patient's medical record, on age at diagnosis, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, or other/unknown), marital status, residential address at diagnosis, stage at diagnosis, tumor size (in cm), lymph node involvement, histology, grade (I, II, III/IV, or unknown), primary source of payment (private only, any Medicaid/military/Other public, Medicare only/Medicare + private, no insurance, and unknown), hormone receptor [estrogen receptor (ER) and progesterone receptor (PR) together referred as hormone receptor (HR), and HER2] status, as well as initial treatment modalities [surgery, radiotherapy, and chemotherapy (endocrine therapy is undercaptured in cancer registry data)]. We followed patients for vital status from linkage with vital records as of December 31, 2014.

We used a multicomponent measure of neighborhood SES (nSES), based on patients' residential census block group at diagnosis. This measure incorporated the 2000 U.S. Census (for cases diagnosed in 2005) and the 2006–2010 American Community Survey data (for cases diagnosed in 2006 and forward) on education, occupation, unemployment, household income, poverty, rent, and house values (15, 16). Each patient was assigned an nSES quintile, based on the distribution of SES across census block groups in California.

Breast cancer tumor subtype definition

We used the breast cancer subtype definition as previously defined (17). Briefly, the CCR has collected information on the expression of ER and PR since 1990 and of HER2 since 1999 (18), with HER2 data completeness increasing greatly after 2005. We classified breast cancers into four mutually exclusive subtype categories: $HR^+/HER2^-$ (defined as ER and/or PR positive and HER2 negative), $HR^+/HER2^+$ (ER and/or PR positive and HER2 positive), $HR^-/HER2^+$ (ER and PR negative and HER2 positive), and triple-negative breast cancer (TNBC, ER, PR, and HER2 negative; refs. 14, 18–21). Of the 160,082 cancers in this analysis, 16,373 (10.2%) did not have information needed to assign to one of these subtypes, including 11,012 cancers (6.9%) for whom only HER2 status was unknown, 631 cancers (0.4%) for whom only HR status was unknown, and 4,730 cancers (3.0%) for whom both HR and HER2 statuses were unknown.

Guideline treatment and receipt of care

Receipt of guideline-concordant care was based on whether women reported receiving treatment that aligned with the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (22) and the American Society of Clinical Oncology Quality Oncology Practice Initiative (23, 24). Cancer registry first course of treatment data on receipt of surgery (lumpectomy, mastectomy, axillary, or sentinel node dissection), radiotherapy, and/or chemotherapy were obtained. Each woman was considered to be in one or more patient subsets based on her age and tumor characteristics (subtype, lymph node involvement, and tumor size). Women with any nonconcordant care were categorized as not receiving guideline treatment. As described in a prior SEER study (25), the subsets were used to define appropriate treatment options (Table 1). Women who did not fall into either subset were classified in regard to guideline concordant treatment as "Not applicable," and those who were in one or more subset but were missing the treatment data needed to determine concordance were classified as "Unknown."

Receiving care at an NCICC was based on diagnosis and/or treatment occurring at such centers. In a population-based setting, because patients may be seen and have received care at multiple facilities, and also due to how the CCR data on multiple reporting facilities are coded, it is not possible to determine the treating facilities.

Statistical analysis

Follow-up time was calculated as the number of days between the date of diagnosis and the earliest of: the date of death from breast cancer (ICD 9/10 = 174/C50), the date of death from another cause, the date of last follow-up (i.e., last known contact), or the study end date (December 31, 2014). The 545 deceased patients with an unknown cause of death were excluded from all models. Cox proportional hazards regression was used to estimate the breast cancer–specific mortality rate ratio (MRR) and corresponding associated 95% CIs for the two age groups with fully adjusted models adjusted for year of diagnosis (continuous), marital status, race/ethnicity, insurance status, nSES, lymph nodes involvement, tumor subtype, tumor size, tumor grade, tumor histology, receipt of guideline concordant treatment, and whether the patient was seen at one or more of the NCICC in California for her breast cancer. Fully adjusted models were additionally adjusted for clustering by block group, using a sandwich estimator of the covariance structure that accounts for intracluster dependence. The proportional hazards assumption was

Table 1. Criteria for determination of receipt of non–guideline-concordant care

Subset	Inclusion criteria	Guideline treatment	Definition of non–guideline-concordant treatment
1	■ Stage I–III ■ Tumor size ≤ 5 cm ■ Not having a diagnosis of Paget disease or inflammatory carcinoma ■ Confirmed pathology ■ Known lymph node involvement ■ Tumor not bilateral ■ No diagnosis of a second primary breast tumor within 60 days	■ Lumpectomy with full course of radiotherapy ■ Mastectomy, with or without radiotherapy	■ No surgery ■ Lumpectomy without radiotherapy ■ Lumpectomy with early discontinuation of radiotherapy
2	■ Stage I–III ■ Age < 70 ■ ER^- and PR^- ■ Tumor size ≥ 1 cm ■ Confirmed pathology	■ Chemotherapy	■ No chemotherapy

examined by statistical testing of the correlation between weighted Schoenfeld residuals and logarithmically transformed survival time. No violations of the assumption were observed, except for AJCC stage at diagnosis. Thus, stage was included as an underlying stratifying variable in the fully adjusted Cox regression models, allowing the baseline hazard to vary by stage. Wald Type 3 tests for interaction between age group (18–49, 50+) and tumor subtype, NCICC, or guideline concordant treatment (excluding Unknown) were computed using cross-product terms, in models adjusted for all statistically significant ($P < 0.05$) interactions with age group (year, insurance status, tumor subtype, NCICC, and guideline concordant treatment). All statistical tests were carried out using SAS software version 9.3 (SAS Institute).

Results

In this population-based study in California ($n = 160{,}082$), 38,509 (24.1%) female patients under the age 50 years at diagnosis presented with stage I to III breast cancer; 121,573 (75.9%) were aged 50 and above. As shown in Table 2, compared with older patients, younger women were more likely to be Hispanic (27% vs. 16%), be married (64% vs. 54%), be covered by private insurance only (76% vs. 54%), have TNBC (13% vs. 10%), be diagnosed with tumors over 2 cm in size (49% vs. 36%), and have ductal tumors (83% vs. 78%). Younger patients were less likely to be diagnosed with stage I cancer (39% vs. 54%), grade I tumors (16% vs. 25%), and negative lymph node involvement (58% vs. 71%) than older patients. No substantial differences were shown for nSES, NCICC status, or guideline concordant treatment between younger and older patients.

Multivariable-adjusted risk of breast cancer mortality for older versus younger patients categorized by 10-year age groups shows that compared with patients ages 40 to 49 years, a progressively higher risk of mortality is shown for older age groups with the highest risk shown in women 80 years and older (MRR = 3.25; 95% CI, 2.98–3.55; Table 3). Results using an age cutoff at 50 years show that older patients had a higher risk of mortality than younger patients (MRR = 1.17; 95% CI, 1.11–1.23).

Breast cancer mortality according to tumor subtype, guideline-appropriate treatment, and receiving care at an NCICC, stratified by age group, is presented in Table 4. Significant interactions between age group and tumor subtype ($P = 0.0008$), NCICC ($P = 0.003$), and guideline-appropriate treatment ($P = 0.015$) were observed. Among younger women, patients with $HR^+/HER2^+$ disease had a lower risk of dying (MRR = 0.80; 95% CI, 0.69–0.93) than those with $HR^+/HER2^-$ tumors, whereas a higher risk was shown for patients with $HR^-/HER2^+$ tumors (MRR = 1.37; 95% CI, 1.15–1.62) and those with TNBC (MRR = 2.50; 95% CI, 2.19–2.86). In older patients, higher mortality was observed for patients with $HR^-/HER2^+$ (MRR = 1.28; 95% CI, 1.14–1.43) and TNBC (MRR = 2.35; 95% CI, 2.17–2.53) but not for $HR^+/HER2^+$ tumors (MRR = 1.05; 95% CI, 0.95–1.15) when compared with women with $HR^+/HER2^-$. Older women who received care at an NCICC had a lower risk of dying from breast cancer than those who did not (MRR = 0.84; 95% CI, 0.76–0.93); no difference was seen in younger patients (MRR = 1.00; 95% CI, 0.89–1.13). In both younger (MRR = 1.20; 95% CI, 1.03–1.40) and older patients (MRR = 1.49; 95% CI, 1.36–1.63), a higher risk of dying was shown for women who did not receive guideline-appropriate treatment, compared with those who did.

Table 5 shows the multivariable-adjusted breast cancer MRRs for older compared with younger patients. Stratified multivariable analyses by tumor subtype showed higher mortality for older compared with younger patients who were diagnosed with $HR^+/HER2^-$ (MRR = 1.24; 95% CI, 1.14–1.35) and with $HR^+/HER2^+$ tumors (MRR = 1.38; 95% CI, 1.17–1.62) but not for those with $HR^-/HER2^+$ (MRR = 0.94; 95% CI, 0.79–1.12) or TNBC (MRR = 1.01; 95% CI, 0.92–1.11). Older women who were not cared for at an NCICC had a higher risk of dying than younger patients (MRR = 1.21; 95% CI, 1.15–1.28), but the opposite was seen among women cared for at an NCICC (MRR = 0.86, 95% CI, 0.73–1.01). Older as compared with younger patients who did not receive guideline-appropriate treatment had a higher risk of dying (MRR = 1.20; 95% CI, 1.02–1.41) but those who had guideline-concordant treatment were not at higher risk (MRR = 1.06; 95% CI, 0.99–1.14).

Discussion

In this large and representative series of women diagnosed with invasive stage I to III breast cancer in California, we found that after taking into account clinical and sociodemographic factors, older patients at diagnosis experience 17% higher breast cancer mortality than younger patients. However, variation in risk was shown according to tumor subtype, receipt of care at an NCICC,

Table 2. Patient demographic and clinical characteristics for younger (18–49 years) and older (50+ years) age at breast cancer diagnosis, California, 2005–2014

	All	Younger (18–49)	Older (50+)
Total number of patients	160,082 (100.0%)	38,509 (100.0%)	121,573 (100.0%)
Age (y), mean (SD)	60.1 (13.6)	42.8 (5.3)	65.6 (10.5)
Age category			
18–39	8,822 (5.5%)	8,822 (22.9%)	
40–49	26,687 (18.5%)	29,687 (77.1%)	
50–59	40,840 (25.5%)		40,840 (33.6%)
60–69	40,163 (25.1%)		40,163 (33.0%)
70–79	25,849 (16.1%)		25,849 (21.3%)
80+	14,721 (9.2%)		14,721 (12.1%)
Race/ethnicity			
Non-Hispanic white	97,459 (60.9%)	18,275 (47.5%)	79,184 (65.1%)
Non-Hispanic black	9,831 (6.1%)	2,581 (6.7%)	7,250 (6.0%)
Hispanic	29,856 (18.7%)	10,502 (27.3%)	19,354 (15.9%)
Asian/Pacific Islander	21,159 (13.2%)	6,714 (17.4%)	14,445 (11.9%)
Other/unknown	1,777 (1.1%)	437 (1.1%)	1,340 (1.1%)
Marital status			
Married	90,433 (56.5%)	24,717 (64.2%)	65,716 (54.1%)
Unmarried	63,794 (39.9%)	12,497 (32.5%)	51,297 (42.2%)
Unknown	5,855 (3.7%)	1,295 (3.4%)	4,560 (3.8%)
Neighborhood (block group) state-wide SES quintile			
1st (lowest)	19,283 (12.0%)	5,041 (13.1%)	14,242 (11.7%)
2nd	27,202 (17.0%)	6,413 (16.7%)	20,789 (17.1%)
3rd	32,684 (20.4%)	7,497 (19.5%)	25,187 (20.7%)
4th	38,182 (23.9%)	9,109 (23.7%)	29,073 (23.9%)
5th (highest)	42,731 (26.7%)	10,449 (27.1%)	32,282 (26.6%)
Insurance status			
Private only	94,291 (58.9%)	29,199 (75.8%)	65,092 (53.5%)
Any Medicaid/military/other public	26,350 (16.5%)	7,701 (20.0%)	18,649 (15.3%)
Medicare only or Medicare + private	33,918 (21.2%)		33,918 (27.9%)
No insurance	1,259 (0.8%)	475 (1.2%)	784 (0.6%)
Unknown	4,264 (2.7%)	1,134 (2.9%)	3,130 (2.6%)
NCICC			
No	143,322 (89.5%)	32,708 (84.9%)	110,614 (91.0%)
Yes	16,760 (10.5%)	5,801 (15.1%)	10,959 (9.0%)
AJCC stage			
I	80,530 (50.3%)	15,002 (39.0%)	65,528 (53.9%)
II	59,779 (37.3%)	16,990 (44.1%)	42,789 (35.2%)
III	19,773 (12.4%)	6,517 (16.9%)	13,256 (10.9%)
Tumor subtype			
$HR^+/HER2^-$	103,807 (64.8%)	22,331 (58.0%)	81,476 (67.0%)
$HR^+/HER2^+$	15,893 (9.9%)	5,235 (13.6%)	10,658 (8.8%)
$HR^-/HER2^+$	7,332 (4.6%)	2,138 (5.6%)	5,194 (4.3%)
Triple negative	16,677 (10.4%)	5,176 (13.4%)	11,501 (9.5%)
Unclassified	16,373 (10.2%)	3,629 (9.4%)	12,744 (10.5%)
Lymph node involvement			
Negative	109,069 (68.1%)	22,478 (58.4%)	86,591 (71.2%)
Positive	50,925 (31.8%)	16,019 (41.6%)	34,906 (28.7%)
Unknown	88 (0.1%)	12 (0.0%)	76 (0.1%)
Tumor size (cm)			
$0.10 < \text{tumor} \leq 0.50$	11,782 (7.4%)	2,343 (6.1%)	9,439 (7.8%)
$0.50 < \text{tumor} \leq 1.00$	27,166 (17.0%)	4,600 (11.9%)	22,566 (18.6%)
$1.00 < \text{tumor} \leq 2.00$	58,110 (36.3%)	12,737 (33.1%)	45,373 (37.3%)
$2.00 < \text{tumor} \leq 5.00$	52,235 (32.6%)	15,080 (39.2%)	37,155 (30.6%)
>5.00	10,789 (6.7%)	3,749 (9.7%)	7,040 (5.8%)
Grade			
Grade I	36,815 (23.0%)	6,141 (15.9%)	30,674 (25.2%)
Grade II	67,075 (41.9%)	14,893 (38.7%)	52,182 (42.9%)
Grade III/IV	50,885 (31.8%)	16,167 (42.0%)	34,718 (28.6%)
Unknown	5,307 (3.3%)	1,308 (3.4%)	3,999 (3.3%)
Histology			
Ductal	126,506 (79.0%)	32,068 (83.3%)	94,438 (77.7%)
Lobular	25,753 (16.1%)	4,805 (12.5%)	20,948 (17.2%)
Other	7,823 (4.9%)	1,636 (4.2%)	6,187 (5.1%)
Guideline-concordant treatment			
Yes	47,057 (29.4%)	15,434 (40.1%)	31,623 (26.0%)
No	8,184 (5.1%)	2,306 (6.0%)	5,878 (4.8%)
Not applicable	104,530 (65.3%)	20,665 (53.7%)	83,865 (69.0%)
Unknown	311 (0.2%)	104 (0.3%)	207 (0.2%)

Table 3. Breast cancer–specific MRRs comparing older with younger age at diagnosis by decade and dichotomized at age 50, California, 2005–2014

Age group	Number of deaths due to breast cancer	MRR (95% CI)[a]	MRR (95% CI)[b]
18–39	723	1.70 (1.56–1.86)	1.20 (1.10–1.32)
40–49	1,513	Referent	Referent
50–59	1,929	0.95 (0.88–1.01)	1.06 (0.99–1.14)
60–69	1,584	0.83 (0.77–0.89)	1.12 (1.04–1.21)
70–79	1,317	1.09 (1.02–1.18)	1.56 (1.43–1.69)
80+	1,403	2.41 (2.24–2.59)	3.25 (2.98–3.55)
18–49	2,236	Referent	Referent
50+	6,233	0.94 (0.90–0.99)	1.17 (1.11–1.23)

[a]Adjusted for year of diagnosis.
[b]Stratified by AJCC stage, and adjusted for year of diagnosis, marital status, race/ethnicity, insurance status, neighborhood SES, lymph node involvement, tumor subtype, tumor size, tumor grade, tumor histology, guideline-concordant treatment, NCICC, and clustering by block group.

and receiving guideline-concordant treatment. The difference in breast cancer mortality between older and younger patients was evident for patients with HR$^+$ tumors regardless of HER2 status, whereas no difference was observed for women with HR$^-$ disease (HR$^-$/HER2$^+$ and TNBC). The higher mortality among older versus younger women was diminished in patients receiving guideline treatment and reversed among those seen at an NCICC, suggesting that appropriate treatment improves survival among older women. Although age differences regarding breast cancer aggressiveness and mortality outcomes have been published (6, 7, 26, 27), to our knowledge no comprehensive reports exist on differences by age for associations between tumor subtype and clinical prognostic factors and breast cancer mortality. In these analyses, we were able to account for a number of sociodemographic and clinical factors as covariates, which provided a comprehensive assessment of age-specific differences in breast cancer mortality.

Presence of aggressive breast tumor subtypes was higher in younger than older women (19.2% HER2$^+$ in younger vs. 13.1% in older patients, and 13.4% TNBC in younger vs. 9.5% in older patients), which is consistent with findings from other studies (28–30). TNBC has been difficult to study before 2005, especially in population settings, since routine HER2 testing for breast cancers was not implemented at large until after Trastuzumab was approved for the adjuvant treatment of early-stage breast cancer in 2005. Comprising less than 20% of breast cancers, TNBC is associated with worse survival than other subtypes, in part due to the lack of targeted therapeutic agents (30, 31). Our study shows that patients diagnosed with TNBC have a greater than 2-fold increased risk of dying compared with those with HR$^+$/HER2$^-$ breast cancer regardless of age group, underscoring the aggressive nature of TNBC subtype.

Stratified analyses by age group showed that among younger patients, patients with HR$^+$/HER2$^+$ tumors had lower risk of dying as compared with those with HR$^+$/HER2$^-$ tumors; older women with HR$^+$/HER2$^+$ tumors had a mortality rate similar to older women with HR$^+$/HER2$^-$ tumors. These findings imply a greater benefit of HER2-targeted treatment (32, 33) on survival in the younger population, who are more likely to be HER2-positive and receive targeted treatment (34). In fact, the most pronounced difference in mortality by age was shown for patients with HR$^+$/HER2$^+$ breast cancer, where older patients had approximately 40% increased risk of breast cancer death relative to younger patients. It is possible that HR$^+$/HER2$^+$ older patients are more likely to forego chemotherapy given the emerging, but understudied, use of dual antiestrogen/anti-HER2 therapy. Conversely, a higher risk of mortality regardless of age group was found for patients with HR$^-$/HER2$^+$ tumors compared with HR$^+$/HER2$^-$ subtype. The results suggest that older women might be sacrificing some potential gain in breast cancer survival to take into account factors such as treatment-related toxicity, functional status, and other quality of life measures. Due to the population-based registry nature of our study, we are unable to assess to what degree these types of trade-offs are being made by the patient or provider.

Table 4. Breast cancer–specific MRRs stratified by age at diagnosis, California, 2005–2014

	Younger (18–49)			Older (50+)		
	Number of deaths due to breast cancer	MRR (95% CI)[a]	MRR (95% CI)[b]	Number of deaths due to breast cancer	MRR (95% CI)[a]	MRR (95% CI)[b]
All	2,236			6,233		
Tumor subtype						
HR$^+$/HER2$^-$	820	Reference	Reference	2,781	Reference	Reference
HR$^+$/HER2$^+$	236	1.11 (0.96–1.29)	**0.80 (0.69–0.93)**	598	**1.69 (1.55–1.85)**	1.05 (0.95–1.15)
HR$^-$/HER2$^+$	214	**2.45 (2.11–2.85**	**1.37 (1.15–1.62)**	476	**2.86 (2.60–3.16)**	**1.28 (1.14–1.43)**
Triple negative	738	**3.88 (3.51–4.29)**	**2.50 (2.19–2.86)**	1,518	**4.26 (4.00–4.54)**	**2.35 (2.17–2.53)**
Unclassified	228	**1.29 (1.11–1.49)**	1.11 (0.96–1.29)	860	**1.56 (1.44–1.68)**	**1.25 (1.16–1.36)**
			P interaction = 0.0008[c]			
NCICC						
No	1,901	Reference	Reference	5,784	Reference	Reference
Yes	335	1.08 (0.96–1.22)	1.00 (0.89–1.13)	449	0.94 (0.86–1.04)	**0.84 (0.76–0.93)**
			P interaction = 0.003[c]			
Guideline-concordant treatment						
Yes	1,409	Reference	Reference	2,879	Reference	Reference
No	230	**1.25 (1.09–1.44)**	**1.20 (1.03–1.40)**	657	**1.47 (1.35–1.60)**	**1.49 (1.36–1.63)**
Not available	590	**0.32 (0.29–0.36)**	1.00 (0.88–1.15)	2,683	**0.31 (0.29–0.32)**	**1.14 (1.05–1.24)**
Unknown	7	0.95 (0.45–2.00)	0.59 (0.27–1.30)	14	1.09 (0.65–1.85)	0.79 (0.45–1.40)
			P interaction = 0.015[c]			

[a]Adjusted for year at diagnosis.
[b]Stratified by AJCC stage, and adjusted for year of diagnosis, age at diagnosis (continuous), marital status, race/ethnicity, insurance status, nSES, lymph node involvement, tumor size, tumor grade, tumor histology, and clustering by block group.
[c]*P* for interaction between age group (younger and older) and tumor subtype, NCICC, or guideline-concordant treatment (excluding unknown) from a model which included all significant interactions with age group.

Published OnlineFirst October 17, 2018; DOI: 10.1158/1055-9965.EPI-18-0353

Table 5. Breast cancer–specific MRRs comparing older with younger age at diagnosis, stratified by tumor subtype, NCICC, and guideline-concordant treatment, California, 2005–2014

	Younger (18–49), number of deaths	Older (50+), number of deaths	MRR (95% CI)[a] Older vs. younger (referent)	MRR (95% CI)[b] Older vs. younger (referent)
Tumor subtype				
$HR^+/HER2^-$	820	2,781	1.00 (0.93–1.08)	1.24 (1.14–1.35)
$HR^+/HER2^+$	236	598	**1.34 (1.15–1.56)**	**1.38 (1.17–1.62)**
$HR^-/HER2^+$	214	476	0.97 (0.82–1.14)	0.94 (0.79–1.12)
Triple negative	738	1,518	0.95 (0.87–1.04)	1.01 (0.92–1.11)
Unclassified	228	860	1.16 (1.00–1.34)	**1.31 (1.12–1.53)**
NCICC				
No	1,901	5,784	0.97 (0.92–1.02)	**1.21 (1.15–1.28)**
Yes	335	449	0.74 (0.64–0.85)	0.86 (0.73–1.01)
Guideline-concordant treatment				
Yes	1,409	2,879	1.04 (0.94–1.10)	1.06 (0.99–1.14)
No	230	657	**1.18 (1.02–1.37)**	**1.20 (1.02–1.41)**
Not available	590	2,683	**1.21 (1.11–1.33)**	**1.34 (1.22–1.47)**

[a]Adjusted for year of diagnosis.
[b]Stratified by AJCC stage and adjusted for year of diagnosis, marital status, race/ethnicity, insurance status, nSES, lymph node involvement, tumor subtype (in models not stratified by this), tumor size, tumor grade, tumor histology, guideline-concordant treatment (in models not stratified by this), NCICC (in models not stratified by this), and clustering by block group.

It has been reported in the literature that older patients with breast cancer receive less guideline-appropriate treatment than their younger counterparts (8, 35, 36). Therefore, our finding of a higher mortality in older than younger patients in women who do not receive guideline-appropriate treatment but not in those who receive guideline-concordant treatment is noteworthy. Our results also show that the higher mortality associated with older compared with younger patients is present among women who were not ever seen at an NCICC and not in patients who received care at an NCICC. As improved breast cancer treatment guideline concordance and surgical outcomes at an NCICC were reported previously (37–39), our findings imply that for older breast cancer patients, which represent the vast majority of the patient population (~80%), receiving care at an NCICC and ensuring that guideline-appropriate treatment is provided will decrease breast cancer mortality in this older age group. Although we could not completely characterize these effects nor do our data allow us to definitively attribute treatment to specific facilities, the better survival outcome for older patients may be due to improved multidisciplinary care coordination, in addition to access to tumor boards, patient-centered care programs, and clinical trials for special geriatric cancer care that may be more achievable in NCICC than in other types of facilities (40, 41). With limited evidence from clinical trials and research studies on older patients due to their comorbid conditions or belief from providers that older patients are incapable of tolerating treatment or have limited long-term benefit, it is difficult to formulate evidence-based treatment and guideline-compliance recommendations.

Our study used CCR data from the most recent decade to examine variation in breast cancer survival in the younger and older groups. Few previous studies have looked concurrently at the age cohorts or have included in the analysis tumor subtypes and receipt of guideline treatment. As the ER, PR, and HER2 designations are becoming increasingly useful in guiding clinical treatment and in breast cancer research (14, 42), however, our conclusions need further validation, as subtypes determined by receptor status serve only as a proxy for full genetic profiling. Also, our survival analyses were adjusted for sociodemographic, clinical characteristics, and first course of cancer-directed treatment, which are available in the cancer registry. However, our study is limited by the lack of data on genetic profile, unmeasured treatment information such as dosing or specific regimens, as well as comorbidities. Consequently, our findings could be subject to residual confounding from incomplete treatment and comorbidity data in the cancer registry (43), which may be especially relevant when comparing older and younger patients. We encourage further population-based studies with more detailed treatment and clinical data and individual-level measures of socioeconomic factors to explore the mechanisms associated with age-specific mortality differences.

In summary, our results based on multivariable-adjusted models show that women age 50 years and older at diagnosis with stage I to III breast cancer have a higher risk of dying from breast cancer compared with younger women, but variation in risk by age exists according to tumor subtype. In addition, the higher mortality rate among older relative to younger women was diminished in women who received guideline-concordant treatment and reversed for patients receiving care at an NCICC, suggesting that ensuring receipt of appropriate treatment and patient-centered care provided in NCICCs may help to reduce age-related differences in breast cancer mortality.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The ideas and opinions expressed herein are those of the author(s) and do not necessarily reflect the opinions of the State of California, Department of Public Health, the NCI, and the Centers for Disease Control and Prevention (CDC) or their Contractors and Subcontractors.

Authors' Contributions

Conception and design: S.L. Gomez, M. Gago-Dominguez, M.E. Martinez
Development of methodology: M.E. Martinez
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.L. Gomez
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.B. Schwab, A.J. Canchola, J.D. Murphy, A.A. Molinolo, M.E. Martinez
Writing, review, and/or revision of the manuscript: R.B. Schwab, Y.S. Miguel, S.L. Gomez, A.J. Canchola, I.K. Komenaka, J.D. Murphy, A.A. Molinolo, M.E. Martinez
Study supervision: S.L. Gomez, M.E. Martinez

Acknowledgments

We would like to thank Valesca Largaespada for her contribution in preparation of the article.

This work was supported by the Specialized Cancer Center Support Grant to the University of California San Diego Moores Cancer Center (CA023100-29 to R. Schwab, M. Gago-Dominguez, J. Murphy, A. Molinolo, and M.E. Martinez) and by the SDSU/UCSD Comprehensive Cancer Center Partnership (CA132379 and CA132384 to Y. San Miguel and M.E. Martinez). The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; CDC's National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the NCI's SEER Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute, Cancer Registry of Greater California.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 4, 2018; revised August 8, 2018; accepted October 10, 2018; published first October 17, 2018.

References

1. Zilliacus EM, Meiser B, Lobb EA, Kirk J, Warwick L, Tucker K. Women's experience of telehealth cancer genetic counseling. J Genet Couns 2010;19:463–72.
2. Robson ME, Storm CD, Weitzel J, Wollins DS, Offit K. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol 2010;28:893–901.
3. Kothari AS, Beechey-Newman N, D'Arrigo C, Hanby AM, Ryder K, Hamed H, et al. Breast carcinoma in women age 25 years or less. Cancer 2002; 94:606–14.
4. Xiong Q, Valero V, Kau V, Kau SW, Taylor S, Smith TL, et al. Female patients with breast carcinoma age 30 years and younger have a poor prognosis: the M.D. Anderson Cancer Center experience. Cancer 2001;92:2523–8.
5. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H. Breast cancer in young women: poor survival despite intensive treatment. PloS One 2009;4:e7695.
6. Maggard MA, O'Connell JB, Lane KE, Liu JH, Etzioni DA, Ko CY. Do young breast cancer patients have worse outcomes? J Surg Res 2003;113:109–13.
7. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am College Surg 2009;208:341–7.
8. Bouchardy C, Rapiti E, Fioretta G, Laissue P, Neyroud-Caspar I, Schafer P, et al. Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol 2003;21:3580–7.
9. Kim J, Durden E. Socioeconomic status and age trajectories of health. Soc Sci Med 2007;65:2489–502.
10. Dannefer D. Cumulative advantage/disadvantage and the life course: cross-fertilizing age and social science theory. J Gerontol B Psychol Sci Soc Sci 2003;58:S327–37.
11. Bernardi D, Errante D, Tirelli U, Salvagno L, Bianco A, Fentiman IS. Insight into the treatment of cancer in older patients: developments in the last decade. Cancer Treat Rev 2006;32:277–88.
12. Siu AL U.S. Preventative Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2016;164:279–96.
13. Morabia A, Costanza MC. International variability in ages at menarche, first livebirth, and menopause. World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Am J Epidemiol 1998;148: 1195–205.
14. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006;295:2492–502.
15. Yost K, Perkins C, Cohen R, Morris C, Wright W. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. Cancer Causes Control 2001;12:703–11.
16. Yang J, Schupp CW, Harrati A, Clarke C, Keegan THM, Gomez SL. Developing an area-based socioeconomic measure from American Community Survey data. Fremont, CA: Cancer Prevention Institute of California; 2014.
17. Tao L, Chu L, Wang LI, Moy L, Brammer M, Song C, et al. Occurrence and outcome of de novo metastatic breast cancer by subtype in a large, diverse population. Cancer Causes Control 2016;27:1127–38.
18. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California Cancer Registry. Cancer 2007;109:1721–8.
19. Bernstein L, Lacey JV Jr.Receptors, associations, and risk factor differences by breast cancer subtypes: positive or negative? J Natl Cancer Inst 2011; 103:451–3.
20. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007;25:118–45.
21. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature 2000;406:747–52.
22. Elledge RM, Clark GM, Chamness GC, Osborne CK. Tumor biologic factors and breast cancer prognosis among white, Hispanic, and black women in the United States. J Nat Cancer Inst 1994;86:705–12.
23. Kurian AW, Lichtensztajn DY, Keegan TH, Leung RW, Shema SJ, Hershman DL, et al. Patterns and predictors of breast cancer chemotherapy use in Kaiser Permanente Northern California, 2004–2007. Breast Cancer Res Treat 2013;137:247–60.
24. Blayney DW, McNiff K, Hanauer D, Miela G, Markstrom D, Neuss M. Implementation of the Quality Oncology Practice Initiative at a university comprehensive cancer center. J Clin Oncol 2009;27:3802–7.
25. Li CI, Malone KE, Daling JR. Differences in breast cancer stage, treatment, and survival by race and ethnicity. Arch Int Med 2003;163:49–56.
26. Zabicki K, Colbert JA, Dominguez FJ, Gadd MA, Hughes KS, Jones JL, et al. Breast cancer diagnosis in women < or = 40 versus 50 to 60 years: increasing size and stage disparity compared with older women over time. Ann Surg Oncol 2006;13:1072–7.
27. Keegan TH, Press DJ, Tao L, DeRouen MC, Kurian AW, Clarke CA, et al. Impact of breast cancer subtypes on 3-year survival among adolescent and young adult women. Breast Cancer Res 2013;15:R95.
28. Cancello G, Maisonneuve P, Rotmensz N, Viale G, Mastropasqua MG, Pruneri G, et al. Prognosis and adjuvant treatment effects in selected breast cancer subtypes of very young women (<35 years) with operable breast cancer. Ann Oncol 2010;21:1974–81.
29. Azim HA Jr., Michiels S, Bedard PL, Singhal SK, Criscitiello C, Ignatiadis M, et al. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clin Cancer Res 2012;18:1341–51.
30. Lund MJ, Trivers KF, Porter PL, Coates RJ, Leyland-Jones B, Brawley OW, et al. Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA. Breast Cancer Res Treat 2009; 113:357–70.
31. O'Brien KM, Cole SR, Tse CK, Perou CM, Carey LA, Foulkes WD, et al. Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. Clin Cancer Res 2010;16:6100–10.
32. Baselga J, Cortes J, Kim SB, Im SA, Hegg R, Im YH, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109–19.
33. Slamon D, Pegram M. Rationale for trastuzumab (Herceptin) in adjuvant breast cancer trials. Semin Oncol 2001;28:13–9.
34. Anderson WF, Katki HA, Rosenberg PS. Incidence of breast cancer in the United States: current and future trends. J Natl Cancer Inst 2011;103: 1397–402.
35. Freedman RA, Vaz-Luis I, Barry WT, Lii H, Lin NU, Winer EP, et al. Patterns of chemotherapy, toxicity, and short-term outcomes for older women

receiving adjuvant trastuzumab-based therapy. Breast Cancer Res Treat 2014;145:491–501.

36. Griggs JJ, Culakova E, Sorbero ME, Poniewierski MS, Wolff DA, Crawford J, et al. Social and racial differences in selection of breast cancer adjuvant chemotherapy regimens. J Clin Oncol 2007;25: 2522–7.
37. Birkmeyer NJ, Goodney PP, Stukel TA, Hillner BE, Birkmeyer JD. Do cancer centers designated by the National Cancer Institute have better surgical outcomes? Cancer 2005;103:435–41.
38. Friese CR, Earle CC, Silber JH, Aiken LH. Hospital characteristics, clinical severity, and outcomes for surgical oncology patients. Surgery 2010;147: 602–9.
39. In H, Neville BA, Lipsitz SR, Corso KA, Weeks JC, Greenberg CC. The role of National Cancer Institute-designated cancer center status: observed variation in surgical care depends on the level of evidence. Ann Surg 2012;255:890–5.
40. Archampong D, Borowski D, Wille-Jorgensen P, Iversen LH. Workload and surgeon's specialty for outcome after colorectal cancer surgery. Cochrane Database Syst Rev 2012:CD005391.
41. Chapman AE, Swartz K, Schoppe J, Arenson C. Development of a comprehensive multidisciplinary geriatric oncology center, the Thomas Jefferson University experience. J Geriatr Oncol 2014;5:164–70.
42. Carlson RW, Allred DC, Anderson BO, Burstein HJ, Carter WB, Edge SB, et al. Breast cancer. Clinical practice guidelines in oncology. J Natl Compr Canc Netw 2009;7:122–92.
43. Giordano SH, Kuo YF, Duan Z, Hortobagyi GN, Freeman J, Goodwin JS. Limits of observational data in determining outcomes from cancer therapy. Cancer 2008;112:2456–66.

Published OnlineFirst October 17, 2018; DOI: 10.1158/1055-9965.EPI-18-0353

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Breast Cancer Mortality in Older and Younger Patients in California

Li Tao, Richard B. Schwab, Yazmin San Miguel, et al.

Cancer Epidemiol Biomarkers Prev 2019;28:303-310. Published OnlineFirst October 17, 2018.