

# UC San Diego

## UC San Diego Previously Published Works

### Title

Breast Cancer Mortality in Older and Younger Breast Cancer Patients in California

### Permalink

<https://escholarship.org/uc/item/91m874wn>

### Journal

Cancer Epidemiology Biomarkers & Prevention, 28(2)

### ISSN

1055-9965

### Authors

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

### Publication Date

2019-02-01

### DOI

10.1158/1055-9965.epi-18-0353

Peer reviewed



# HHS Public Access

Author manuscript

*Cancer Epidemiol Biomarkers Prev.* Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

*Cancer Epidemiol Biomarkers Prev.* 2019 February ; 28(2): 303–310. doi:  
10.1158/1055-9965.EPI-18-0353.

## Breast Cancer Mortality in Older and Younger Patients in California

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

<sup>1</sup>Greater Bay Area Cancer Registry, Cancer Prevention Institute of California, Fremont, CA

<sup>2</sup>Moore's Cancer Center, University of California, San Diego, La Jolla, CA

<sup>3</sup>Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA

<sup>4</sup>Maricopa Medical Center, Phoenix, AZ

<sup>5</sup>Family Medicine and Public Health, University of California, San Diego, La Jolla, CA

<sup>6</sup>Fundación Galega Medicina Genómica, Instituto de Investigación Sanitaria de Santiago IDIS, Santiago de Compostela, Spain

<sup>7</sup>Department of Epidemiology and Biostatistics, University of California, San Francisco, CA

### Abstract

**Introduction:** 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-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 a National Cancer Institute-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).

---

Corresponding Author: Maria Elena Martinez, University of California, San Diego, Moore's Cancer Center, 3855 Health Sciences Dr., #0901, La Jolla, CA 92093-0901, Phone: (858) 822-3638, emartinez@ucsd.edu.

**Conflict of Interest:** The authors declare no potential conflicts of interest.

**Conclusions:** While 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 a NCICC.

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

### Keywords

breast cancer; mortality; younger and older patients; breast tumor subtype

---

### Introduction

Breast cancer is the most common cancer among women worldwide, accounting for a fifth of overall cancer mortality (1). In the United States (U.S.), 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 to 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 Program reported that younger compared to older breast cancer patients had higher breast cancer mortality, with hazard ratios of 1.095 (95% confidence interval [CI] = 1.101 – 1.183) comparing patients less than 35 to those 50–55 years of age in one study (6) and 1.39 (CI, 1.34 to 1.45) in the second study comparing women <40 to 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 vs. older patients include later stage disease, more aggressive tumors, and less favorable tumor receptor status in younger than older patients (5, 6). However, biological factors, under-treatment, and socioeconomic (SES) factors may potentially result in higher mortality among older compared to 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, while 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 are 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-2000's 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 mortality differences vary by tumor subtype, receiving guideline-appropriate care, and receiving care at a National Cancer Institute-designated cancer center (NCICC).

## 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 AJCC (American Joint Committee on Cancer) Stage I-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 (NHW), non-Hispanic black, Hispanic, Asian/Pacific Islander, or other/unknown], marital status, residential address at diagnosis, stage at diagnosis, tumor size (in centimeters [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 (ER) and progesterone receptor (PR)-together referred as hormone receptor (HR), and human epidermal growth factor receptor 2 (HER2)] status, as well as initial treatment modalities [surgery, radiation, and chemotherapy (endocrine therapy is under-captured in cancer registry data)]. We followed patients for vital status from linkage with vital records as of December 31, 2014.

We used a multi-component measure of neighborhood socioeconomic status (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 a 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) (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 status 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), radiation, 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 non-concordant care were categorized as not receiving guideline treatment. As described in a prior Surveillance, Epidemiology, and End Results (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 regards 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 a 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 (12/31/2014). 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% confidence intervals (CI) 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 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, NCICCC, 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, NCICCC, 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-III breast cancer; 121,573 (75.9%) were aged 50 and above. As shown in Table 2, compared to older patients, younger women were more likely to be Hispanic (27% versus 16%), married (64% versus 54%), covered by private insurance only (76% versus 54%), have TNBC (13% versus 10%), be diagnosed with tumors over 2 cm in size (49% versus 36%), and to have ductal tumors (83% versus 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, NCICCC 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 to patients aged 40–49 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 cut-off 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 a NCICCC, stratified by age group are presented in Table 4. Significant interactions between age group and tumor subtype ( $P = 0.0008$ ), NCICCC ( $P = 0.003$ ), 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, while 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 to women with HR+/HER2-. Older women who received care at a NCICCC 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 to those who did.

Table 5 shows the multivariable-adjusted breast cancer MRRs for older compared to younger patients. Stratified multivariable analyses by tumor subtype showed higher mortality for older compared to 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 a 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 a 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-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 a NCICC, 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, while 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 a NCICC, suggesting that appropriate treatment improves survival among older women. While 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 analysis, 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 versus 13.1% in older patients, and 13.4% TNBC in younger versus 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 ~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 anti-estrogen/anti-HER2 therapy. Conversely, a higher risk of mortality regardless of age group, was found for patients with HR-/HER2+ tumors compared to 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 type of trade-offs are being made by the patient or provider.

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 to younger patients is present among women who were not ever seen at a NCICC and not in patients who received care at a NCICC. As improved breast cancer treatment guideline concordance and surgical outcomes at a NCICC were reported previously (37–39), our findings imply that for older breast cancer patients, which represents the vast majority of the patient population (~80%), receiving care at a 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 California Cancer Registry 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-III breast cancer have a higher risk of dying from breast cancer compared to younger women but variation in risk by age exist 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 a 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.

## Acknowledgement

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

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; Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the National Cancer Institute's Surveillance, Epidemiology and End Results 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 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 National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors.

## 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. [PubMed: 20411313]
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. [PubMed: 20065170]
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. [PubMed: 11857291]
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. [PubMed: 11745185]
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. [PubMed: 19907646]
6. Maggard MA, O'Connell JB, Lane KE, Liu JH, Etzioni DA, Ko CY. Do young breast cancer patients have worse outcomes? *The Journal of surgical research.* 2003;113:109–13. [PubMed: 12943818]
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. *Journal of the American College of Surgeons.* 2009;208:341–7. [PubMed: 19317994]

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. [PubMed: 12913099]
9. Kim J, Durden E. Socioeconomic status and age trajectories of health. *Soc Sci Med.* 2007;65:2489–502. [PubMed: 17765375]
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. [PubMed: 14614120]
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. [PubMed: 16698183]
12. Siu AL, Force USPST. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med.* 2016;164:279–96. [PubMed: 26757170]
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. [PubMed: 9867266]
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. [PubMed: 16757721]
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 : CCC.* 2001;12:703–11. [PubMed: 11562110]
16. Yang J, Schupp CW, Harrati A, Clarke C, Keegan THM, Gomez SL. Developing an area-based socioeconomic measure from American Community Survey data. Cancer Prevention Institute of California, Fremont, 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. [PubMed: 27496200]
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. [PubMed: 17387718]
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. [PubMed: 21346225]
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. [PubMed: 17159189]
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. [PubMed: 10963602]
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. *Journal of the National Cancer Institute.* 1994;86:705–12. [PubMed: 7908990]
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 research and treatment.* 2013;137:247–60. [PubMed: 23139057]
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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27:3802–7. [PubMed: 19487377]
25. Li CI, Malone KE, Daling JR. Differences in breast cancer stage, treatment, and survival by race and ethnicity. *Archives of internal medicine.* 2003;163:49–56. [PubMed: 12523916]
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. [PubMed: 16865599]

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 research : BCR*. 2013;15:R95. [PubMed: 24131591]
28. Canello 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. [PubMed: 20332136]
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. [PubMed: 22261811]
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. [PubMed: 18324472]
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. [PubMed: 21169259]
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. [PubMed: 22149875]
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. [PubMed: 21753181]
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. [PubMed: 24756187]
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. [PubMed: 17577029]
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. [PubMed: 15622523]
38. Friese CR, Earle CC, Silber JH, Aiken LH. Hospital characteristics, clinical severity, and outcomes for surgical oncology patients. *Surgery*. 2010;147:602–9. [PubMed: 20403513]
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. [PubMed: 22504278]
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. [PubMed: 22419309]
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. [PubMed: 24495585]
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. [PubMed: 19200416]
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. [PubMed: 18428196]

**Table 1.**

## Criteria for Determination of Receipt of Non-Guideline-Concordant Care

Subset	Inclusion Criteria	Guideline Treatment	Definition of Non-Guideline-Concordant Treatment
1	<ul style="list-style-type: none"> <li>▪ Stage I-III</li> <li>▪ Tumor size ≤ 5 cm</li> <li>▪ Not having a diagnosis of Paget disease or inflammatory carcinoma</li> <li>▪ Confirmed pathology</li> <li>▪ Known lymph node involvement</li> <li>▪ Tumor not bilateral</li> <li>▪ No diagnosis of a second primary breast tumor within 60 days</li> </ul>	<ul style="list-style-type: none"> <li>▪ Lumpectomy with full-course of radiation</li> <li>▪ Mastectomy, with or without radiation</li> </ul>	<ul style="list-style-type: none"> <li>▪ No surgery</li> <li>▪ Lumpectomy without radiation</li> <li>▪ Lumpectomy with early discontinuation of radiation</li> </ul>
2	<ul style="list-style-type: none"> <li>▪ Stage I-III</li> <li>▪ Age &lt;70</li> <li>▪ ER- and PR-</li> <li>▪ Tumor size ≥ 1cm</li> <li>▪ Confirmed pathology</li> </ul>	<ul style="list-style-type: none"> <li>▪ Chemotherapy</li> </ul>	<ul style="list-style-type: none"> <li>▪ No chemotherapy</li> </ul>

**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+)	
<b>Total Number of Patients</b>	160,082	100.0%	38,509	100.0%	121,573	100.0%
<b>Age (yrs) Mean (SD)</b>	60.1 (13.6)		42.8 (5.3)		65.6 (10.5)	
<b>Age category</b>						
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%
<b>Race/ethnicity</b>						
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%
<b>Marital status</b>						
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%
<b>Neighborhood (block group) statewide SES quintile</b>						
1st (lowest)	19,283	12.0%	5,041	13.1%	14,242	11.7%
2 <sup>nd</sup>	27,202	17.0%	6,413	16.7%	20,789	17.1%
3 <sup>rd</sup>	32,684	20.4%	7,497	19.5%	25,187	20.7%
4 <sup>th</sup>	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%
<b>Insurance status</b>						
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%
<b>National Cancer Institute--designated cancer center</b>						
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%
<b>AJCC Stage</b>						

	All		Younger (18–49)		Older (50+)	
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%
<b>Tumor subtype</b>						
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%
<b>Lymph node involvement</b>						
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%
<b>Tumor size (cm)</b>						
0.10 < tumor 0.50	11,782	7.4%	2,343	6.1%	9,439	7.8%
0.50 < tumor 1.00	27,166	17.0%	4,600	11.9%	22,566	18.6%
1.00 < tumor 2.00	58,110	36.3%	12,737	33.1%	45,373	37.3%
2.00 < tumor 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%
<b>Grade</b>						
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%
<b>Histology</b>						
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%
<b>Guideline concordant treatment</b>						
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 mortality rate ratios comparing older to younger age at diagnosis by decade and dichotomized at age 50, California, 2005–2014

Age group	No. deaths due to breast cancer	MRR (95 % CI) *	MRR (95 % CI) **
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)

\* Adjusted for year of diagnosis

\*\* 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, NCI-designated cancer center, and clustering by block group.

**Table 4.** Breast cancer specific mortality rate ratios stratified by age at diagnosis, California, 2005–2014

	Younger (18–49)		Older (50+)	
	No. deaths due to breast cancer	MRR (95%CI)*	No. deaths due to breast cancer	MRR (95%CI)*
All	2,236		6,233	
<b>Tumor Subtype</b>				
HR+/HER2-	820	Reference	2,781	Reference
HR+/HER2+	236	1.11 (0.96–1.29)	598	<b>1.69 (1.55–1.85)</b>
HR-/HER2+	214	<b>2.45 (2.11–2.85)</b>	476	<b>2.86 (2.60–3.16)</b>
Triple negative	738	<b>3.88 (3.51–4.29)</b>	1,518	<b>2.35 (2.17–2.53)</b>
Unclassified	228	<b>1.29 (1.11–1.49)</b>	860	<b>1.56 (1.44–1.68)</b>
<i>P-interaction = 0.0008***</i>				
<b>National Cancer Institute-designated cancer center</b>				
No	1,901	Reference	5,784	Reference
Yes	335	1.08 (0.96–1.22)	449	0.94 (0.86–1.04)
<i>P-interaction = 0.003***</i>				
<b>Guideline concordant treatment</b>				
Yes	1,409	Reference	2,879	Reference
No	230	<b>1.25 (1.09–1.44)</b>	657	<b>1.47 (1.35–1.60)</b>
Not available	590	<b>0.32 (0.29–0.36)</b>	2,683	<b>0.31 (0.29–0.32)</b>
Unknown	7	0.95 (0.45–2.00)	14	1.09 (0.65–1.85)
<i>P-interaction = 0.015***</i>				

\* Adjusted for year at diagnosis.

\*\* 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.

\*\*\* P for interaction between age group (younger and older) and tumor subtype, NCI cancer center, or guideline concordant treatment (excluding unknown) from a model which included all significant interactions with age group.



**Table 5.**

Breast cancer specific mortality rate ratios comparing older to younger age at diagnosis, stratified by tumor subtype, National Cancer Institute-designated cancer center, and guideline concordant treatment, California, 2005–2014

	Younger (18–49) No. deaths	Older (50+) No. deaths	MRR (95% CI)* Older vs. Younger (referent)	MRR (95% CI)** Older vs. Younger (referent)
<b>Tumor Subtype</b>				
HR+/HER2–	820	2,781	1.00 (0.93–1.08)	<b>1.24 (1.14–1.35)</b>
HR+/HER2+	236	598	<b>1.34 (1.15–1.56)</b>	<b>1.38 (1.17–1.62)</b>
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)	<b>1.31 (1.12–1.53)</b>
<b>National Cancer Institute-designated cancer center</b>				
No	1,901	5,784	0.97 (0.92–1.02)	<b>1.21 (1.15–1.28)</b>
Yes	335	449	0.74 (0.64–0.85)	0.86 (0.73–1.01)
<b>Guideline concordant treatment</b>				
Yes	1,409	2,879	1.04 (0.94–1.10)	1.06 (0.99–1.14)
No	230	657	<b>1.18 (1.02–1.37)</b>	<b>1.20 (1.02–1.41)</b>
Not available	590	2,683	<b>1.21 (1.11–1.33)</b>	<b>1.34 (1.22–1.47)</b>

\* Adjusted for year of diagnosis.

\*\* 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), NCI-designated cancer center (in models not stratified by this), and clustering by block group.