Breast cancer mortality in African-American and non-Hispanic white women by molecular subtype and stage at diagnosis: a population-based study

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Abstract

Background—Higher breast cancer mortality rates for African-American than non-Hispanic white women are well documented; however, it remains uncertain if this disparity occurs in disease subgroups defined by tumor molecular markers and stage at diagnosis. We examined racial differences in outcome according to subtype and stage in a diverse, population-based series of 103,498 patients.

Methods—We obtained data for all invasive breast cancers diagnosed 1/1/2005-12/31/2012 and followed through 12/31/2012 among 93,760 non-Hispanic white and 9,738 African-American women in California. Molecular subtypes were categorized according to tumor expression of hormone receptor (HR, based on estrogen and progesterone receptors) and human epidermal growth factor receptor 2 (HER2). Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer-specific mortality.

Results—After adjustment for patient, tumor and treatment characteristics, outcomes were comparable by race for Stage I or IV cancer regardless of subtype, and HR+/HER2+ or HR-/HER2+ cancer regardless of stage. We found substantially higher hazards of breast cancer death among African-American women with Stage II/III HR+/HER2- (HR, 1.31, 95% CI, 1.03-1.65, and HR, 1.39, 95% CI, 1.10-1.75, respectively) and Stage III triple-negative cancers relative to whites.

Conclusions—There are substantial racial/ethnic disparities among patients with Stages II/III HR+/HER2- and Stage III triple-negative breast cancers but not for other subtype and stage.

Impact—These data provide insights to assess barriers to targeted treatment (e.g. trastuzumab or endocrine therapy) of particular subtypes of breast cancer among African-American patients.

Keywords

Disparity; breast cancer; subtype; stage; mortality

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Introduction

Although breast cancer mortality rates have declined in the United States over the past few decades (1), African-American women experience substantially higher breast cancer mortality than non-Hispanic white (white) women (2, 3). The mortality disparity is especially noteworthy in light of the lower incidence rate of breast cancer among African-American than white women (4, 5) .

This racial/ethnic disparity in breast cancer outcomes has been well studied and prior studies have set forth biological and non-biological explanations for the mortality difference (6-9). African-American women are more likely to be diagnosed at a later stage of breast cancer than whites, which may be due to factors such as limited primary care (10) or longer follow-up time after an abnormal or inconclusive screening mammogram (11, 12). Poorer survival also may be influenced by patient social context disproportionately affecting African-American women, specifically socioeconomic deprivation at the individual or neighborhood levels, and social injustice (13, 14). However, there is also evidence that, relative to white women, breast cancer among African-American women may be biologically more aggressive and more likely to express molecular markers [i.e. estrogen receptor (ER) and progesterone receptor (PR) (together referred to as hormone receptor (HR)), and human epidermal growth factor receptor 2 (HER2)] associated with worse outcomes (7, 15-17). In particular, African-American women are more likely than white women to be diagnosed with triple-negative breast cancer, which, because of its lack of expression for the three molecular markers, does not currently have targeted treatment options (7, 15-17). A few studies have measured the contribution of molecular subtype to racial/ethnic disparities in breast cancer survival (18-20), but the findings were inconsistent when comparing survival in African-American patients with whites. One study found mortality risk difference between African-American and white women occurs only among older women diagnosed with luminal A/p53- but not with triple-negative breast cancer (18), whereas another two studies suggested higher overall mortality (19) and breast cancer specific mortality (20) in African-American than white patients with the triple-negative subtype. To date, there have been no datasets large enough to examine racial/ethnic mortality disparities by tumor molecular subtypes and stage at diagnosis, the two important prognostic determinants of survival, to further isolate the subgroups with the worst disparities.

We took advantage of the California Cancer Registry, for which breast cancers defined by ER, PR and HER2 status are reported for a particularly large and racially/ethnically diverse population to study overall and breast-cancer specific mortality among white and African-American women diagnosed with invasive breast cancer during the period 2005-2012. We assessed whether mortality differences persisted across molecular subtype and stage at diagnosis, defined jointly. We also assessed the contributions of clinical and demographic characteristics, including first course of treatment, neighborhood socioeconomic status (SES), and health insurance status, to racial/ethnic mortality differences.

Materials and Methods

Study Population

We obtained from the California Cancer Registry (CCR) information about all 104,051 white or African-American female California residents 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, with the following histological subtypes of breast carcinoma or adenocarcinoma: 8000, 8010, 8020, 8022, 8050, 8140, 8201-8230, 8255, 8260, 8401, 8453, 8480-8530, and 8575] between 1/1/2005 and 12/31/2012. We excluded patients who were diagnosed by mammography/xerography (n = 51) or death certificate/autopsy only (n=502). The final study population included 103,498 patients, of whom 93,760 were white and 9,738 were African-American. For each patient, we obtained information routinely abstracted from the medical record on age at diagnosis, race/ethnicity (white and African-American), census-block group of residence, AJCC stage at diagnosis [I, II, III, IV, or unstaged /not applicable (NA)], tumor size [in centimeters (cm), microinvasion, diffuse, or unknown], grade (low, high, or unknown), primary source of payment at the time of initial diagnosis and/or treatment (public insurance, private insurance, no insurance/self-pay, and insurance status unknown), ER, PR and HER2 tumor expression status, as well as treatment modalities [surgery, radiation, chemotherapy (endocrine therapy, although available, is under-captured in cancer registry data)] received within the first 12 months after diagnosis. We also obtained vital status as of 12/31/2012 (maximum follow-up of 7 years) and the underlying cause of death for the deceased. This project was overseen by the Institutional Review Board of the Cancer Prevention Institute of California.

In addition, because individual patient-level SES information is not collected by the CCR, we developed a multi-component measure of neighborhood SES based on patients' residential census block group at diagnosis, incorporating 2000 U.S. Census (for cases diagnosed in 2005) and 2006-2010 American Community Survey data (for cases diagnosed 2006+) on education, occupation, unemployment, household income, poverty, rent, and house values (21, 22). Patient residential address at diagnosis was geocoded to a census block group. In our study, 1.6% of all cases could not be geocoded due to incomplete address. Each patient was assigned a neighborhood SES quintile, based on the distribution of SES across census block groups in California.

Breast cancer subtype definition

The CCR has collected information on the expression of ER and PR since 1990 and of HER2 since 1999 (23). Before 2005, 41% of cases lacked HER2 data, but data completeness has increased to at least 83% since that time. Because of the reduced reliability of HER2 receptor status (17) and data completeness prior to 2005, we limited our analyses to between 2005 and 2011, the most recent years for which more complete data were available. Each marker was reported as positive, negative, borderline, not tested/ recorded, or unknown, based on the medical record information recorded by the reporting facility. We classified the breast cancers into four mutually exclusive subtype categories: HR+/HER2- was defined as ER or PR positive and HER2 negative; HR+/HER2+ as ER or PR positive and HER2 positive; HR-/HER2+ as ER and PR negative and HER2 positive; and triple-negative as ER,

PR, and HER2 negative (7, 17, 23-25). Of the 103,498 cancers, 14,287 (13.8%) did not have information needed to assign to one of these subtypes, including 8,597 cancers (8.3%) for whom only HER2 status was unknown, 608 cancers (0.6%) for whom only HR status was unknown, and 5,690 cancers (5.5%) for whom both HR and HER2 status were unknown. Cancers for which subtype was missing did not differ statistically significantly with respect to patient race/ethnicity from those for which subtype was known.

Statistical Analysis

The Mantel-Haenszel chi-square test was used to compute *P*-values for differences in distribution of patient and clinical characteristics between white and African-American patients. Cox proportional hazards regression was used to estimate hazard ratios (HR) and corresponding associated 95% confidence intervals (CI) with independent variables added in turn to understand their individual effects. The Kaplan-Meier method and the log-rank test were used to show and test differences in overall survival for patients diagnosed at each stage by breast cancer subtype.

For deceased patients, survival time was measured in days from the date of diagnosis to the date of death from breast cancer. Patients who died from other causes were censored at the time of death. Patients alive at the study end date (12/312012) were censored at this time or at the date of last follow-up (i.e., last known contact). 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. Given that proportional hazards varied by stage at diagnosis (AJCC Stage I-IV and unknown), it was included as a stratifying variable in all Cox regression models, allowing the baseline hazard to vary by stage. All models were adjusted for clustering by block group. Ninety-eight percent of censored patients had a follow-up date within 2 years of the study end date; the proportion of patients without recent follow-up information did not differ by race/ethnicity nor by neighborhood SES.

Cells with fewer than five cases are not shown for privacy purposes. All statistical tests were carried out using SAS software version 9.3 (SAS Institute, Cary, North Carolina). All *P*-values reported were two-sided, and those that were <0.05 were considered to be statistically significant.

Results

In this population-based cohort of 93,760 white and 9,738 African-American breast cancer patients, the mean (± standard deviation) age at diagnosis was higher for white (62.3 ±13.6 years) than African-American women (58.8 ±13.7 years). Compared to whites, African-American patients were more likely to be diagnosed at a younger age, to be unmarried, to live in lower SES neighborhoods, to be diagnosed at a more advanced stage, to have larger tumors, and to have public insurance or no insurance (all *P*s < 0.05, Table 1). Approximately 20% of African-American, while only 10% white patients were diagnosed with triple-negative breast cancer.

After a mean follow-up time of 3.5 (±2.3) years, African-American patients had an 18% overall increased risk of death from breast cancer (HR, 1.18, 95% CI, 1.10-1.27) compared to white patients after including stage as a stratifying variable and adjusting for molecular subtype, age at diagnosis, marital status, tumor characteristics, treatment modalities, neighborhood SES, and insurance status (data not shown on table). This deficit in breast cancer specific survival was observed across all molecular subtypes (all $P_{\text{log-rank}} < 0.01$, Figure 1). After adjusting for tumor characteristics and first course of treatment, African-American women with HR+/HER2- and triple-negative breast cancer had a significantly higher hazard of breast cancer death compared with whites (HR, 1.29, 95% CI, 1.14-1.45 for HR+/HER2- and HR, 1.22, 95% CI, 1.08-1.39 for triple-negative breast cancer, models 1 and 2, Table 2). After further adjustment with neighborhood SES and insurance status (models 3 and 4, Table 2), African-American women with HR+/HER2- and triple-negative breast cancer consistently showed elevated hazard of breast cancer-specific death (HR, 1.27, 95% CI, 1.12-1.43 and HR, 1.21, 95% CI, 1.06-1.37, respectively), compared with white patients.

When analyses were stratified by stage at diagnosis, we found worse breast cancer survival in African-American women diagnosed within Stage II-IV for HR+/HER2- and triple-negative breast cancers, and Stage III for HR-/HER2+ breast cancers (all $P_{\text{log-rank}} < 0.05$), but not in any other subgroups defined jointly by molecular subtype and stage (all $P_{\text{log-rank}} > 0.05$, figures not shown). There were no differences in breast cancer specific mortality between African-American and white patients within HR-/HER2+ breast cancer regardless of stage, and Stage I and IV breast cancer regardless of molecular subtype, even after adjustment for all prognostic factors, including age, marital status, tumor characteristics, treatment, neighborhood SES and insurance status (stage stratified model 4, Table 2). However, higher mortality remained for African-Americans compared with whites for some molecular subtype/stage subgroups. Among Stages II and III HR+/HER2- patients, African-American women experienced significantly increased risk of breast cancer specific death [HR (95%CI) 1.31 (1.03-1.65) and 1.39 (1.10-1.75), for Stage II and III patients, respectively], comparing to white women. Also, in patients diagnosed with Stage III triple-negative breast cancer, African-American women had a 37% (95% CI, 1.05-1.55) higher hazard of breast cancer death relative to whites.

Discussion

In this large, representative series of women diagnosed with invasive breast cancer in California in recent years, we found that disparities in breast cancer mortality between African-Americans and whites varied according to molecular subtype and stage of the tumor. Within Stages II and III HR+/HER2- breast cancer, we found 31-39% higher rate of breast cancer specific death in African-American than white patients after adjustment for demographic factors, tumor characteristics, first course of treatment, neighborhood SES, and insurance status. However, these factors, especially neighborhood SES, fully explained overall mortality differences in Stage I HR+/HER2-, Stage I and II HR+/HER2+, and Stage II triple-negative breast cancer (data not shown), suggesting critical roles for early detection and early diagnosis in efforts to eliminate disparities. This finding is consistent with prior reports of a substantial impact of neighborhood SES on racial disparities in breast cancer

mortality (26-29). In this California cohort, a much higher proportion of African-American patients were diagnosed with triple-negative breast cancer, a more aggressive subtype (19, 30), than whites. Our study sets forth Stages II and III HR+/HER2- and Stage III triple-negative breast cancers as particularly important areas for research to identify additional biological tumor characteristics and non-biological factors that may contribute to the racial/ethnic disparity. Prior studies focusing on triple-negative breast cancer reported that molecular factors, including hereditary gene expressions, alterations in p53 and genomic copy number, tumor DNA methylation status, and mutations in DNA repair genes (31-34), as well as epidemiological factors, including reproductive and patient demographic factors (35), differed in prevalence among racial groups. These data are not yet reported to cancer registries, and thus, the extent to which they may explain survival disparities is not yet fully understood.

Our primary finding of disparities occurring in certain breast cancer patient subgroups, which included the subtype with available targeted therapies (36) and the early stages curable by adequate treatment, is noteworthy. Specifically, study suggests that African-Americans are primarily and persistently at higher risk of death only for HR+/HER2- breast cancers at Stages II and III, for which breast cancers respond favorably to anti-endocrine therapy or trastuzumab therapy (37). This underscores the central role of treatment in the black/white disparity in breast cancer, even though no race/ethnicity differences in adjuvant hormone therapy use were identified in two recent studies (38, 39). Unfortunately, information on endocrine therapies is under-captured in cancer registry data, and specific information regarding receipt of trastuzumab is not reported. Cancer registry first course of treatment data do not include information on specific components of chemotherapy, nor aspects such as timing, dosage, completion of regimen, guideline adherence, or details on the specific types of surgery, radiation, endocrine, or chemotherapy agents.

Other non-biological factors and factors independent of stage at presentation, such as residual treatment/healthcare differences due to social and health system factors, may also explain a significant portion of the mortality disparity. Racial/ethnic differences in receipt of treatment may exist even among those with insurance, and may be attributable to patient (e.g., comorbidities) factors, healthcare system factors, or differences in tumor biology or response to treatments. African-American women are less likely to receive adequately dosed, timely and appropriate administration of chemotherapy (40-43), and adjuvant radiation therapy after breast-conserving surgery (44, 45). Historically underserved populations, including African-Americans, generally benefit less from medical advances (46). It remains to be seen whether the shift towards more personalized treatment options based in gene expression testing/profiling, including evolving HER2-directed and anti-endocrine therapies, will result in more pronounced mortality disparities for African-Americans. Deficiencies in treatment and care among African-American breast cancer patients may result from a number of contributing causes. While health insurance status is the most referenced and an important barrier (47-49), a number of additional factors, such as out-of-pocket financial hardship caused by cancer care (50), need for time taken from work (51), and problems with travel (52, 53), may also disproportionally affect the cancer treatment and care of African-American women. In addition, the nuanced role of patient-physician communication, which is understood to affect physicians' care recommendations

and patients' compliance with treatment (54), is also relevant, as African-American patients have been reported to have more misunderstandings about treatment (55, 56) and lower satisfaction or trust of the health care system (57). Thus, although overall, the quality of breast cancer care is improving and mortality rates is declining, disparities still remain, such that African-Americans may still receive insufficient, poorer-quality, and diminished access to care as compared to whites (10).

Our study has the strength of being population-based with large numbers of African-American and white cases to enable examination of breast cancer mortality across combinations of subtypes and stage. While we did adjust outcomes according to available demographic and clinical characteristics, we lacked clinical information on detailed regimens for treatment and treatments received after the first course. Another limitation is our inability to control for individual-level measures of SES, like level of education or income. While neighborhood and individual SES are strongly correlated, neighborhood SES under-estimates associations observed with individual-level markers (58). Furthermore, our mean follow-up was 3.5 years (and our maximum 8 years), because of the recency of HER2 data availability; thus, our results cannot speak to longer-term survival. However, it has been reported that the disparity in breast cancer mortality between African-Americans and NH whites is more pronounced during the first few years after diagnosis (59). Regardless, studies with longer follow-up are warranted.

In summary, we found an important mortality disparity between African-Americans and NH whites within the relatively curable subtypes of Stages II and III HR+/HER2- and Stage III triple-negative breast cancers after consideration of demographic, treatment, tumor characteristics, neighborhood SES, and insurance status. Our study suggests that healthcare delivery differences due to social and health system factors may contribute to the mortality disparity, given the importance of optimally targeted therapy to curing tumors of these stages and subtypes. Future research should assess biomedical, contextual and individual-level factors leading to inadequate treatment of African-American women with Stages II and III HR+/HER2- cancers and Stage III triple-negative breast cancers.

Acknowledgments

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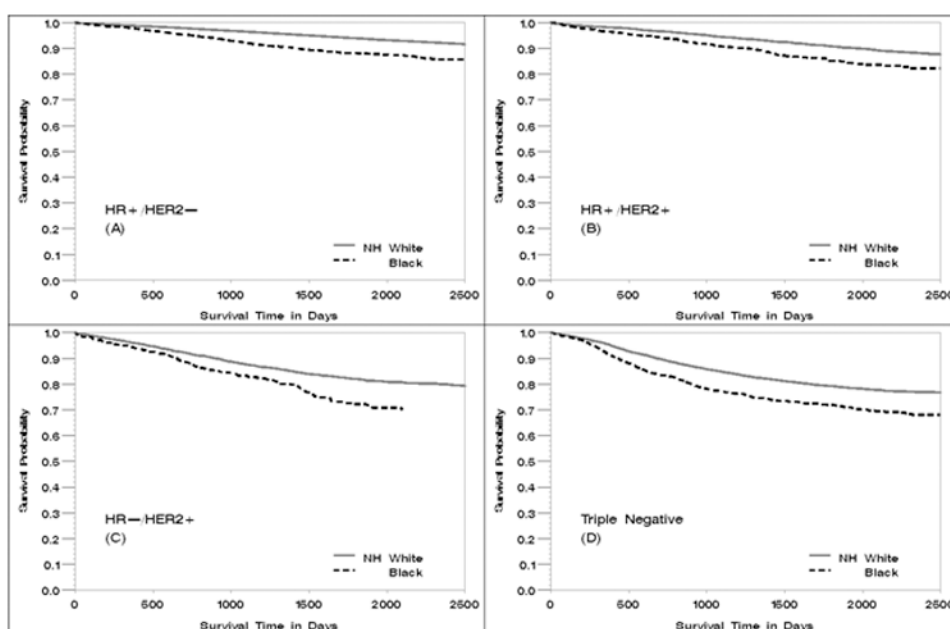
Figure 1.
Breast cancer-specific survival for non-Hispanic White and African-American patients by breast cancer subtype, California 2005-2012. All $P_{log\text{-}rank} < 0.01$
The vertical axis represents survival probability; the horizontal axis represents survival time in days. A) HR+/HER2- ; B) HR+/HER2+; C) HR-/HER2+ ; D) Triple Negative.

Table 1

Demographic and clinical characteristics for white and African-American women diagnosed with invasive breast cancer, California, 2005-2012

	Non-Hispanic White Total N (n=93,760) (%)	African-American Total N (n=9,738) (%)
Patient demographic characteristics		
Age at diagnosis		
<45 years	8680 (9.3%)	1448 (14.9%)
45-49 years	9146 (9.8%)	1216 (12.5%)
50-54 years	10935 (11.7%)	1333 (13.7%)
55-59 years	12036 (12.8%)	1344 (13.8%)
60-64 years	12787 (13.6%)	1212 (12.4%)
65+	40176 (42.8%)	3185 (32.7%)
Marital status at diagnosis		
Married	51828 (55.3%)	3313 (34.0%)
Never married	12789 (13.6%)	3036 (31.2%)
Previously married	25959 (27.7%)	2997 (30.8%)
Unknown	3184 (3.4%)	392 (4.0%)
Neighborhood SES in quintile		
1, lowest	7054 (7.5%)	2543 (26.1%)
2	13944 (14.9%)	2472 (25.4%)
3	19294 (20.6%)	2066 (21.2%)
4	24110 (25.7%)	1680 (17.3%)
5, highest	29358 (31.3%)	977 (10.0%)
Tumor characteristics Subtype [1]		
HR+/HER2-	59341 (63.3%)	4813 (49.4%)
HR+/HER2+	8474 (9.0%)	1050 (10.8%)
HR-/HER2+	3913 (4.2%)	527 (5.4%)
Triple negative	8589 (9.2%)	1896 (19.5%)
Unclassified	13443 (14.3%)	1452 (14.9%)
AJCC stage at diagnosis		
I	45503 (48.5%)	3542 (36.4%)
II	29803 (31.8%)	3472 (35.7%)
III	10330 (11.0%)	1500 (15.4%)
IV	4291 (4.6%)	731 (7.5%)
Unknown/unstaged	3833 (4.1%)	493 (5.1%)
Tumor Grade [2]		
Low	61032 (65.1%)	4689 (48.2%)
High	26374 (28.1%)	4325 (44.4%)
Unknown	6354 (6.8%)	724 (7.4%)
Lymph node involvement		
Negative	61967 (66.1%)	5567 (57.2%)

	Non-Hispanic White Total N (n=93,760) (%)	African-American Total N (n=9,738) (%)
Positive	29150 (31.1%)	3806 (39.1%)
Unknown	2643 (2.8%)	365 (3.7%)
Size		
0-2.00 cm	54913 (58.6%)	4526 (46.5%)
2.01-5.00 cm	27256 (29.1%)	3359 (34.5%)
>5.00 cm	6393 (6.8%)	1117 (11.5%)
Microinvasion	435 (0.5%)	94 (1.0%)
Diffuse	886 (0.9%)	113 (1.2%)
Unknown	3877 (4.1%)	529 (5.4%)
Insurance status [3]		
Private	57025 (60.8%)	5435 (55.8%)
Medicare	16827 (17.9%)	956 (9.8%)
Military	672 (0.7%)	118 (1.2%)
Public/Medicaid	15350 (16.4%)	2822 (29.0%)
Uninsured/self-pay	624 (0.7%)	139 (1.4%)
Unknown	3262 (3.5%)	268 (2.8%)
Surgery		
No	6711 (7.2%)	1114 (11.4%)
Yes	86544 (92.3%)	8586 (88.2%)
Unknown	505 (0.5%)	38 (0.4%)
Chemotherapy		
No	58310 (62.2%)	4923 (50.6%)
Yes	33889 (36.1%)	4663 (47.9%)
Unknown	1561 (1.7%)	152 (1.6%)
Radiation therapy		
No	48195 (51.4%)	5567 (57.2%)
Yes	45463 (48.5%)	4165 (42.8%)
Unknown	102 (0.1%)	6 (0.1%)

[1] Human epidermal growth factor receptor 2 (HER2), hormone receptor (HR), triple-negative (estrogen-receptor negative, progesterone- receptor, and human epidermal growth factor receptor 2)

[2] Low grade was defined as tumor grade I and II; high grade was defined as tumor grade IIII and IV.

[3] Public insurance included Medicaid and other government-assisted programs; and private insurance included health maintenance organizations, preferred provider organizations, managed care not otherwise specified, and military care.

Table 2

Breast cancer specific-mortality [showing HR (95% CI)] for white and African-American women diagnosed with invasive breast cancer, by subtype, California, 2005-2012

Variables in model	HR+/HER2-	HR+/HER2+	HR-/HER2+	Triple-Negative
All patients				
Model 1 [1]	1.51 (1.34-1.70)	1.25 (1.00-1.57)	1.28 (1.01-1.62)	1.34 (1.19-1.51)
Model 2 [1]	1.39 (1.24-1.57)	1.23 (0.97-1.54)	1.24 (0.97-1.57)	1.31 (1.16-1.48)
Model 3 [1]	1.29 (1.14-1.45)	1.09 (0.86-1.39)	1.15 (0.90-1.47)	1.22 (1.08-1.39)
Model 4 [1]	1.27 (1.12-1.43)	1.06 (0.84-1.35)	1.09 (0.85-1.39)	1.21 (1.06-1.37)
AJCC stage I				
Model 1	1.26 (0.83-1.92)	2.00 (0.83-4.80)	1.11 (0.43-2.87)	1.02 (0.68-1.55)
Model 2	1.12 (0.73-1.71)	1.75 (0.71-4.28)	1.06 (0.41-2.76)	1.00 (0.66-1.52)
Model 3	1.03 (0.67-1.58)	1.31 (0.51-3.37)	1.08 (0.40-2.90)	0.85 (0.55-1.30)
Model 4	1.02 (0.66-1.56)	1.38 (0.53-3.56)	1.00 (0.37-2.70)	0.83 (0.54-1.28)
AJCC stage II				
Model 1	1.56 (1.24-1.96)	1.36 (0.87-2.12)	1.39 (0.82-2.35)	1.22 (1.00-1.51)
Model 2	1.44 (1.14-1.80)	1.36 (0.87-2.14)	1.24 (0.73-2.11)	1.24 (1.00-1.53)
Model 3	1.32 (1.05-1.67)	1.23 (0.77-1.95)	1.09 (0.63-1.88)	1.23 (0.99-1.54)
Model 4	1.31 (1.03-1.65)	1.27 (0.80-2.02)	0.95 (0.55-1.66)	1.19 (0.95-1.49)
AJCC stage III				
Model 1	1.53 (1.22-1.92)	1.27 (0.83-1.93)	1.41 (0.97-2.06)	1.59 (1.30-1.95)
Model 2	1.45 (1.16-1.82)	1.18 (0.77-1.81)	1.34 (0.91-1.97)	1.49 (1.22-1.82)
Model 3	1.41 (1.12-1.78)	1.03 (0.66-1.61)	1.31 (0.88-1.96)	1.38 (1.12-1.70)
Model 4	1.39 (1.10-1.75)	1.03 (0.65-1.61)	1.30 (0.87-1.95)	1.37 (1.11-1.70)
AJCC stage IV				
Model 1	1.47 (1.19-1.82)	1.01 (0.67-1.52)	1.17 (0.74-1.84)	1.26 (0.94-1.70)
Model 2	1.36 (1.10-1.69)	1.05 (0.70-1.60)	1.12 (0.71-1.79)	1.24 (0.92-1.67)
Model 3	1.24 (1.00-1.54)	0.98 (0.64-1.51)	1.12 (0.70-1.81)	1.17 (0.86-1.59)
Model 4	1.24 (1.00-1.54)	0.89 (0.57-1.37)	1.01 (0.62-1.65)	1.08 (0.79-1.48)

[1] AJCC stage was included as a stratifying variable in these models, allowing the underlying hazard function to vary by stage.

Note: BCS = Breast Cancer Specific

Model 1: Adjusted for age at diagnosis (continuous), marital status, and basic tumor characteristics [tumor grade (low/high/unknown), tumor size (in cm, continuous), and lymph node involvement (yes/no)]

Model 2: Model 1 + Treatment [surgery (yes/no), chemotherapy (yes/no), and radiation therapy (yes/no)]

Model 3: Model 2 + Neighborhood SES in quintile

Model 4: Model 3 + Insurance status (public insurance, private insurance, no insurance/self-pay, and insurance status unknown)