Research Article

Cancer Epidemiology, Biomarkers & Prevention

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 between January 1, 2005, and December 31, 2012, and followed through December 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 relative hazard (RH) 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 $HR^+/HER2^-$ (RH, 1.31; 95% CI, 1.03–1.65; and RH, 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. *Cancer Epidemiol Biomarkers Prev; 24(7); 1039–45. ©2015 AACR.*

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 biologic and non-biologic 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 that 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 (BCS) mortality (20) in African-American than White patients with the triple-negative subtype. To date,

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doi: 10.1158/1055-9965.EPI-15-0243

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 BCS 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 histologic subtypes of breast carcinoma or adenocarcinoma: 8000, 8010, 8020, 8022, 8050, 8140, 8201–8230, 8255, 8260, 8401, 8453, 8480–8530, and 8575] between January 1, 2005 and December 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 undercaptured in cancer registry data)] received within the first 12 months after diagnosis. We also obtained vital status as of December 1, 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 the 2000 U.S. Census (for cases diagnosed in 2005) and 2006–2010 American Community Survey data (for cases diagnosed after 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 before 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 χ^2 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 relative hazard (RH) 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 (12/31/2012) 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). 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

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 y	8,680 (9.3%)	1,448 (14.9%)
45–49 y	9,146 (9.8%)	1,216 (12.5%)
50–54 y	10,935 (11.7%)	1,333 (13.7%)
55–59 y	12,036 (12.8%)	1,344 (13.8%)
60–64 y	12,787 (13.6%)	1,212 (12.4%)
65+	40,176 (42.8%)	3,185 (32.7%)
Marital status at diagnosis		
Married	51,828 (55.3%)	3,313 (34.0%)
Never married	12,789 (13.6%)	3,036 (31.2%)
Previously married	25,959 (27.7%)	2,997 (30.8%)
Unknown	3,184 (3.4%)	392 (4.0%)
Neighborhood SES in quintile		
1, lowest	7,054 (7.5%)	2,543 (26.1%)
2	13,944 (14.9%)	2,472 (25.4%)
3	19,294 (20.6%)	2,066 (21.2%)
4	24,110 (25.7%)	1,680 (17.3%)
5, highest	29,358 (31.3%)	977 (10.0%)
Tumor characteristics		
Subtype[a]		
$HR^+/HER2^-$	59,341 (63.3%)	4,813 (49.4%)
$HR^+/HER2^+$	8,474 (9.0%)	1,050 (10.8%)
$HR^-/HER2^+$	3,913 (4.2%)	527 (5.4%)
Triple negative	8,589 (9.2%)	1,896 (19.5%)
Unclassified	13,443 (14.3%)	1,452 (14.9%)
AJCC stage at diagnosis		
I	45,503 (48.5%)	3,542 (36.4%)
II	29,803 (31.8%)	3,472 (35.7%)
III	10,330 (11.0%)	1,500 (15.4%)
IV	4,291 (4.6%)	731 (7.5%)
Unknown/unstaged	3,833 (4.1%)	493 (5.1%)
Tumor grade[b]		
Low	61,032 (65.1%)	4,689 (48.2%)
High	26,374 (28.1%)	4,325 (44.4%)
Unknown	6,354 (6.8%)	724 (7.4%)
Lymph node involvement		
Negative	61,967 (66.1%)	5,567 (57.2%)
Positive	29,150 (31.1%)	3,806 (39.1%)
Unknown	2,643 (2.8%)	365 (3.7%)
Size		
0–2.00 cm	54,913 (58.6%)	4,526 (46.5%)
2.01–5.00 cm	27,256 (29.1%)	3,359 (34.5%)
>5.00 cm	6,393 (6.8%)	1,117 (11.5%)
Microinvasion	435 (0.5%)	94 (1.0%)
Diffuse	886 (0.9%)	113 (1.2%)
Unknown	3,877 (4.1%)	529 (5.4%)
Insurance status[c]		
Private	57,025 (60.8%)	5,435 (55.8%)
Medicare	16,827 (17.9%)	956 (9.8%)
Military	672 (0.7%)	118 (1.2%)
Public/Medicaid	15,350 (16.4%)	2,822 (29.0%)
Uninsured/self-pay	624 (0.7%)	139 (1.4%)
Unknown	3,262 (3.5%)	268 (2.8%)
Surgery		
No	6,711 (7.2%)	1,114 (11.4%)
Yes	86,544 (92.3%)	8,586 (88.2%)
Unknown	505 (0.5%)	38 (0.4%)
Chemotherapy		
No	58,310 (62.2%)	4,923 (50.6%)
Yes	33,889 (36.1%)	4,663 (47.9%)
Unknown	1,561 (1.7%)	152 (1.6%)
Radiotherapy		
No	48,195 (51.4%)	5,567 (57.2%)
Yes	45,463 (48.5%)	4,165 (42.8%)
Unknown	102 (0.1%)	6 (0.1%)

[a]HER2, hormone receptor (HR), triple-negative (estrogen-receptor negative, progesterone-receptor, and human epidermal growth factor receptor 2).
[b]Low grade was defined as tumor grade I and II; high grade was defined as tumor grade IIII and IV.
[c]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.

deviation) age at diagnosis was higher for White (62.3 ± 13.6 years) than African-American women (58.8 ± 13.7 years). Compared with 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 $P < 0.05$, Table 1). Approximately 20% of African-American, whereas 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 (RH, 1.18; 95% CI, 1.10–1.27) compared with 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 BCS survival was observed across all molecular subtypes (all $P_{\text{log-rank}} < 0.01$, Fig. 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–related death compared with Whites (RH, 1.29; 95% CI, 1.14–1.45 for $HR^+/HER2^-$; and RH, 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 BCS death (RH, 1.27; 95% CI, 1.12–1.43; and RH, 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 BCS 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

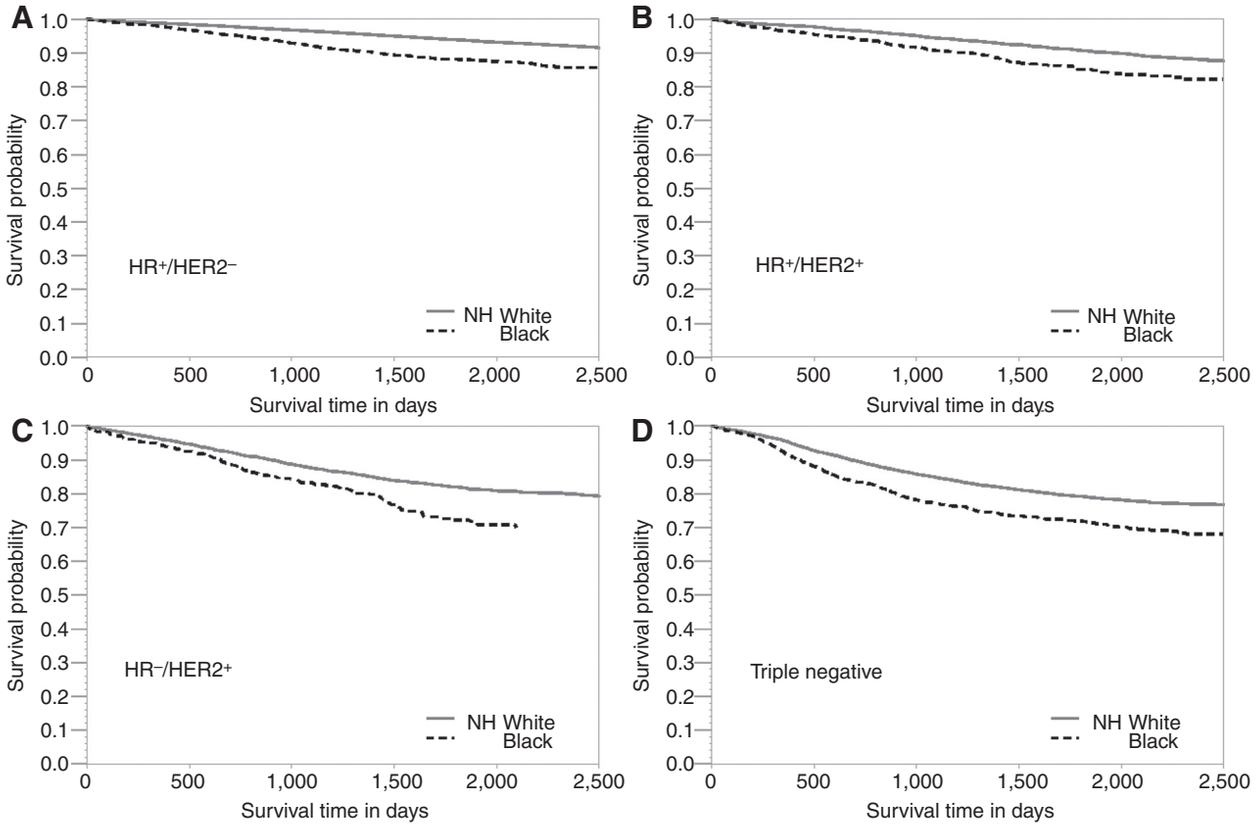

Figure 1.
BCS survival for non-Hispanic White and African-American patients by breast cancer subtype, California 2005–2012. Vertical axis, survival probability; horizontal axis, survival time (days). A, $HR^+/HER2^-$; B, $HR^+/HER2^+$; C, $HR^-/HER2^+$; D, triple negative.

increased risk of BCS death [RH, 1.31; 95% CI, 1.03–1.65; and RH, 1.39; 95% CI, 1.10–1.75, for stage II and III patients, respectively], comparing with 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–related 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% to 39% higher rate of BCS 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 biologic tumor characteristics and nonbiologic 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 epidemiologic 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 antiendocrine 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

Table 2. BCS mortality [showing RH (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[a]	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[a]	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[a]	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[a]	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)

NOTE: 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 radiotherapy (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).

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

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 nonbiologic 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 radiotherapy 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 toward more personalized treatment options based in gene expression testing/profiling, including evolving HER2-directed and antiendocrine 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. Although 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 with 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. Although 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. Although 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 non-Hispanic 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 non-Hispanic 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.

Disclosure of Potential Conflicts of Interest

S.L. Gomez and C.A. Clarke report receiving commercial research grants from Genentech. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The ideas and opinions expressed herein are those of the authors and endorsement by the State of California, Department of Health Services, the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.L. Gomez, C.A. Clarke
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Tao, A.W. Kurian, C.A. Clarke
Writing, review, and/or revision of the manuscript: L. Tao, S.L. Gomez, T.H.M. Keegan, A.W. Kurian, C.A. Clarke
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.A. Clarke
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Grant Support

This study was funded by the Stanford Cancer Institute (to C.A. Clarke) and the National Cancer Institute's Surveillance, Epidemiology, and End Results Program under contract HHSN2612010000140C (to L. Tao, S.L. Gomez, and T.H.M. Keegan). The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology, and End Results Program under contract HHSN2612010000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #1U58 DP000807-01 awarded to the Public Health Institute.

Received March 4, 2015; revised April 29, 2015; accepted May 5, 2015; published OnlineFirst May 12, 2015.

References

1. Jatoi I, Chen BE, Anderson WF, Rosenberg PS. Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. J Clin Oncol 2007;25:1683–90.
2. Tammemagi CM, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D. Comorbidity and survival disparities among black and white patients with breast cancer. JAMA 2005;294:1765–72.
3. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Fay MP, Feuer EJ, Edwards BK (eds). SEER Cancer Statistics Review, 1975–2000, National Cancer Institute. Bethesda, MD; 2003. Available from: http://seer.cancer.gov/csr/1975_2000/.
4. Joslyn SA, Foote ML, Nasseri K, Coughlin SS, Howe HL. Racial and ethnic disparities in breast cancer rates by age: NAACCR Breast Cancer Project. Breast Cancer Res Treat 2005;92:97–105.
5. Smigal C, Jemal A, Ward E, Cokkinides V, Smith R, Howe HL, et al. Trends in breast cancer by race and ethnicity: update 2006. CA Cancer J Clin 2006;56:168–83.
6. Maskarinec G, Sen C, Koga K, Conroy SM. Ethnic differences in breast cancer survival: status and determinants. Womens Health 2011;7:677–87.
7. 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.
8. Ooi SL, Martinez ME, Li CI. Disparities in breast cancer characteristics and outcomes by race/ethnicity. Breast Cancer Res Treat 2011;127:729–38.
9. Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. J Natl Cancer Inst 2005;97:439–48.
10. Silber JH, Rosenbaum PR, Clark AS, Giantonio BJ, Ross RN, Teng Y, et al. Characteristics associated with differences in survival among black and white women with breast cancer. JAMA 2013;310:389–97.
11. Chang SW, Kerlikowske K, Napoles-Springer A, Posner SF, Sickles EA, Perez-Stable EJ. Racial differences in timeliness of follow-up after abnormal screening mammography. Cancer 1996;78:1395–402.
12. Jones BA, Dailey A, Calvocoressi L, Reams K, Kasl SV, Lee C, et al. Inadequate follow-up of abnormal screening mammograms: findings from the race differences in screening mammography process study (United States). Cancer Causes Control 2005;16:809–21.
13. Gerend MA, Pai M. Social determinants of Black-White disparities in breast cancer mortality: a review. Cancer Epidemiol Biomarkers Prev 2008;17:2913–23.
14. Newman LA, Griffith KA, Jatoi I, Simon MS, Crowe JP, Colditz GA. Meta-analysis of survival in African American and white American patients with breast cancer: ethnicity compared with socioeconomic status. J Clin Oncol 2006;24:1342–9.
15. Beverly LN, Flanders WD, Go RC, Soong SJ. A comparison of estrogen and progesterone receptors in black and white breast cancer patients. Am J Public Health 1987;77:351–3.
16. Newman LA. Breast cancer in African-American women. Oncologist 2005;10:1–14.
17. 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.
18. Ma H, Lu Y, Malone KE, Marchbanks PA, Deapen DM, Spirtas R, et al. Mortality risk of black women and white women with invasive breast cancer by hormone receptors, HER2, and p53 status. BMC Cancer 2013;13:225.
19. 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.
20. Sachdev JC, Ahmed S, Mirza MM, Farooq A, Kronish L, Jahanzeb M. Does race affect outcomes in triple negative breast cancer? Breast Cancer (Auckl) 2010;4:23–33.
21. 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.
22. 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. Available at http://www.cpic.org/cancer-registry/cancer-surveillance/acs-ses-report.aspx.

23. 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.
24. 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.
25. 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.
26. Bradley CJ, Given CW, Roberts C. Race, socioeconomic status, and breast cancer treatment and survival. J Natl Cancer Inst 2002;94:490–6.
27. Brawley OW. Disaggregating the effects of race and poverty on breast cancer outcomes. J Natl Cancer Inst 2002;94:471–3.
28. Baquet CR, Commiskey P. Socioeconomic factors and breast carcinoma in multicultural women. Cancer 2000;88:1256–64.
29. Parise CA, Caggiano V. Disparities in race/ethnicity and socioeconomic status: risk of mortality of breast cancer patients in the California Cancer Registry, 2000–2010. BMC Cancer 2013;13:449.
30. 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.
31. Jones BA, Kasl SV, Howe CL, Lachman M, Dubrow R, Curnen MM, et al. African-American/White differences in breast carcinoma: p53 alterations and other tumor characteristics. Cancer 2004;101:1293–301.
32. Loo LW, Wang Y, Flynn EM, Lund MJ, Bowles EJ, Buist DS, et al. Genome-wide copy number alterations in subtypes of invasive breast cancers in young white and African American women. Breast Cancer Res Treat 2011;127:297–308.
33. Wang S, Dorsey TH, Terunuma A, Kittles RA, Ambs S, Kwabi-Addo B. Relationship between tumor DNA methylation status and patient characteristics in African-American and European-American women with breast cancer. PLoS ONE 2012;7:e37928.
34. Martin DN, Boersma BJ, Yi M, Reimers M, Howe TM, Yfantis HG, et al. Differences in the tumor microenvironment between African-American and European-American breast cancer patients. PLoS One 2009;4:e4531.
35. Anders C, Carey LA. Understanding and treating triple-negative breast cancer. Oncology 2008;22:1233–9; discussion 9–40, 43.
36. Alvarez RH, Valero V, Hortobagyi GN. Emerging targeted therapies for breast cancer. J Clin Oncol 2010;28:3366–79.
37. Hudis CA, Gianni L. Triple-negative breast cancer: an unmet medical need. Oncologist 2011;16 Suppl 1:1–11.
38. Livaudais JC, Li C, John EM, Terry MB, Daly M, Buys SS, et al. Racial and ethnic differences in adjuvant hormonal therapy use. J Womens Health 2012;21:950–8.
39. Livaudais JC, Lacroix A, Chlebowski RT, Li CI, Habel LA, Simon MS, et al. Racial/ethnic differences in use and duration of adjuvant hormonal therapy for breast cancer in the women's health initiative. Cancer Epidemiol Biomarkers Prev 2013;22:365–73.
40. Bickell NA, Wang JJ, Oluwole S, Schrag D, Godfrey H, Hiotis K, et al. Missed opportunities: racial disparities in adjuvant breast cancer treatment. J Clin Oncol 2006;24:1357–62.
41. Dignam JJ. Efficacy of systemic adjuvant therapy for breast cancer in African-American and Caucasian women. J Natl Cancer Inst Monogr 2001;30:36–43.
42. Griggs JJ, Sorbero ME, Stark AT, Heininger SE, Dick AW. Racial disparity in the dose and dose intensity of breast cancer adjuvant chemotherapy. Breast Cancer Res Treat 2003;81:21–31.
43. 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.
44. Riley GF, Potosky AL, Klabunde CN, Warren JL, Ballard-Barbash R. Stage at diagnosis and treatment patterns among older women with breast cancer: an HMO and fee-for-service comparison. JAMA 1999;281:720–6.
45. Mandelblatt JS, Kerner JF, Hadley J, Hwang YT, Eggert L, Johnson LE, et al. Variations in breast carcinoma treatment in older medicare beneficiaries: is it black or white. Cancer 2002;95:1401–14.
46. Nelson A. Unequal treatment: confronting racial and ethnic disparities in health care. J Natl Med Assoc 2002;94:666–8.
47. American Cancer Society. Cancer Facts and Figures for African Americans 2011—2012. Atlanta, GA: American Cancer Society; 2011.
48. Greenwald HP, O'Keefe S, Dicamillo M. The importance of public sector health care in an underserved population. J Health Hum Serv Adm 2004;27:142–57.
49. Ward E, Halpern M, Schrag N, Cokkinides V, DeSantis C, Bandi P, et al. Association of insurance with cancer care utilization and outcomes. CA Cancer J Clin 2008;58:9–31.
50. Moore KA. Breast cancer patients' out-of-pocket expenses. Cancer Nurs 1999;22:389–96.
51. Chirikos TN, Russell-Jacobs A, Jacobsen PB. Functional impairment and the economic consequences of female breast cancer. Women Health 2002;36:1–20.
52. Athas WF, Adams-Cameron M, Hunt WC, Amir-Fazli A, Key CR. Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. J Natl Cancer Inst 2000;92:269–71.
53. Lamont EB, Hayreh D, Pickett KE, Dignam JJ, List MA, Stenson KM, et al. Is patient travel distance associated with survival on phase II clinical trials in oncology? J Natl Cancer Inst 2003;95:1370–5.
54. Hebert-Croteau N, Brisson J, Latreille J, Rivard M, Abdelaziz N, Martin G. Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer. J Clin Oncol 2004;22:3685–93.
55. Lannin DR, Mathews HF, Mitchell J, Swanson MS, Swanson FH, Edwards MS. Influence of socioeconomic and cultural factors on racial differences in late-stage presentation of breast cancer. JAMA 1998;279:1801–7.
56. Lannin DR, Mathews HF, Mitchell J, Swanson MS. Impacting cultural attitudes in African-American women to decrease breast cancer mortality. Am J Surg 2002;184:418–23.
57. LaVeist TA, Carroll T. Race of physician and satisfaction with care among African-American patients. J Natl Med Assoc 2002;94:937–43.
58. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am J Public Health 1992;82:703–10.
59. Menashe I, Anderson WF, Jatoi I, Rosenberg PS. Underlying causes of the black-white racial disparity in breast cancer mortality: a population-based analysis. J Natl Cancer Inst 2009;101:993–1000.