Breast Cancer Mortality in African-American and Non-Hispanic White Women by Molecular Subtype and Stage at Diagnosis: A Population-Based Study

Li Tao¹, Scarlett Lin Gomez¹,², Theresa H.M. Keegan¹,², Allison W. Kurian²,³, and Christina A. Clarke¹,²

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,
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 nor for those from which subtype was known.

Statistical analysis

The Mantel–Haenszel χ² 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 logartihmically 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
Mortality Disparities by Breast Cancer Subtype and Stage

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 effect 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 HER2-negative 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 rega...
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...
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 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, involving 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 disproportionately 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.

### Table 2. BCS mortality (showing RH [95% CI]) for White and African-American women diagnosed with invasive breast cancer, by subtype, California, 2005-2012

<table>
<thead>
<tr>
<th>Variables in model</th>
<th>HR /HER2</th>
<th>HR /HER2</th>
<th>HR /HER2</th>
<th>Triple-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1*</td>
<td>1.51(1.34-1.70)</td>
<td>1.25(1.00-1.57)</td>
<td>1.28(1.01-1.62)</td>
<td>1.34(1.19-1.51)</td>
</tr>
<tr>
<td>Model 2*</td>
<td>1.39(1.24-1.57)</td>
<td>1.23(0.97-1.54)</td>
<td>1.24(0.97-1.57)</td>
<td>1.31(1.16-1.48)</td>
</tr>
<tr>
<td>Model 3*</td>
<td>1.29(1.14-1.45)</td>
<td>1.09(0.86-1.39)</td>
<td>1.15(0.90-1.47)</td>
<td>1.22(1.08-1.39)</td>
</tr>
<tr>
<td>Model 4*</td>
<td>1.27(1.12-1.45)</td>
<td>1.06(0.84-1.35)</td>
<td>1.09(0.85-1.39)</td>
<td>1.21(1.06-1.37)</td>
</tr>
<tr>
<td>AJCC stage I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.26(0.83-1.92)</td>
<td>2.00(0.83-4.80)</td>
<td>1.11(0.43-2.87)</td>
<td>1.02(0.68-1.55)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.12(0.73-1.71)</td>
<td>1.75(0.71-4.28)</td>
<td>1.06(0.41-2.76)</td>
<td>1.00(0.66-1.52)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.03(0.67-1.58)</td>
<td>1.31(0.51-3.37)</td>
<td>1.08(0.40-2.90)</td>
<td>0.85(0.55-1.30)</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.02(0.66-1.56)</td>
<td>1.38(0.55-5.56)</td>
<td>1.00(0.37-2.70)</td>
<td>0.83(0.54-1.28)</td>
</tr>
<tr>
<td>AJCC stage II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.56(1.24-1.96)</td>
<td>1.36(0.87-2.12)</td>
<td>1.39(0.82-2.35)</td>
<td>1.22(1.00-1.51)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.44(1.13-1.80)</td>
<td>1.36(0.87-2.14)</td>
<td>1.24(0.75-2.17)</td>
<td>1.24(1.00-1.53)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.32(1.05-1.67)</td>
<td>1.23(0.77-1.95)</td>
<td>1.09(0.63-1.88)</td>
<td>1.23(0.99-1.54)</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.31(1.05-1.65)</td>
<td>1.27(0.80-2.02)</td>
<td>0.95(0.55-1.66)</td>
<td>1.19(0.95-1.49)</td>
</tr>
<tr>
<td>AJCC stage III</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.53(1.22-1.92)</td>
<td>1.27(0.83-1.93)</td>
<td>1.41(0.97-2.06)</td>
<td>1.59(1.30-1.95)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.45(1.16-1.82)</td>
<td>1.18(0.77-1.81)</td>
<td>1.34(0.91-1.97)</td>
<td>1.49(1.22-1.82)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.41(1.12-1.78)</td>
<td>1.03(0.66-1.61)</td>
<td>1.31(0.88-1.96)</td>
<td>1.38(1.12-1.70)</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.39(1.10-1.75)</td>
<td>1.03(0.65-1.61)</td>
<td>1.30(0.87-1.95)</td>
<td>1.37(1.11-1.70)</td>
</tr>
<tr>
<td>AJCC stage IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.47(1.19-1.82)</td>
<td>1.01(0.67-1.52)</td>
<td>1.17(0.74-1.84)</td>
<td>1.26(0.94-1.70)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.36(1.10-1.69)</td>
<td>1.05(0.70-1.60)</td>
<td>1.12(0.71-1.79)</td>
<td>1.24(0.92-1.67)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.24(1.00-1.54)</td>
<td>0.98(0.64-1.53)</td>
<td>1.12(0.70-1.81)</td>
<td>1.17(0.86-1.59)</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.24(1.00-1.54)</td>
<td>0.89(0.57-1.37)</td>
<td>1.01(0.62-1.65)</td>
<td>1.08(0.79-1.48)</td>
</tr>
</tbody>
</table>

**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).

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

References


Breast Cancer Mortality in African-American and Non-Hispanic White Women by Molecular Subtype and Stage at Diagnosis: A Population-Based Study

Li Tao, Scarlett Lin Gomez, Theresa H.M. Keegan, et al.

Cancer Epidemiol Biomarkers Prev 2015;24:1039-1045. Published OnlineFirst May 12, 2015.

Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-15-0243

This article cites 56 articles, 19 of which you can access for free at:
http://cebp.aacrjournals.org/content/24/7/1039.full.html#ref-list-1

This article has been cited by 1 HighWire-hosted articles. Access the articles at:
/content/24/7/1039.full.html#related-urls

Sign up to receive free email-alerts related to this article or journal.

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.