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Racial Disparities in Breast Cancer Diagnosis and Treatment by Hormone Receptor and HER2 Status

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Abstract

Background: African American and Hispanic women are more likely to be diagnosed with aggressive forms of breast cancer. Disparities within each subtype of breast cancer have not been well documented.

Methods: Using data from 18 SEER cancer registries, we identified 102,064 women aged 20 years or older, diagnosed with invasive breast cancer in 2010–2011, and with known stage, hormone receptor (HR), and HER2 status. Associations between race/ethnicity and cancer stage and receipt of guideline-concordant treatment were evaluated according to HR/HER2 status.

Results: Overall, African American and Hispanic women were 30% to 60% more likely to be diagnosed with stage II–IV breast cancer compared with non-Hispanic whites. African American women had 40% to 70% higher risks of stage IV breast cancer across all four subtypes. American Indian/Alaska Native women had a 3.9-fold higher risk of stage IV triple-negative breast cancer. African American and Hispanic whites were 30% to 40% more likely to receive non–guideline-concordant treatment for breast cancer overall and across subtypes.

Conclusions: Women in several racial/ethnic groups are more likely to be diagnosed with more advanced stage breast cancer. African American and American Indian/Alaska Native women in particular had the highest risk of being diagnosed with stage IV triple-negative breast cancer. African American and Hispanic women were also consistently at higher risk of not receiving guideline-concordant treatment across subtypes.

Impact: These findings provide important characterization of which subtypes of breast cancer racial/ethnic disparities in stage and treatment persist. *Cancer Epidemiol Biomarkers Prev; 24(11); 1666–72. ©2015 AACR.*

Introduction

It has been consistently observed that minority women, especially African Americans, Hispanic whites, and American Indians, are more likely to be diagnosed at more advanced stages of breast cancer (1–3), less likely to receive recommended treatment regimens (1, 3, 4), and more likely to have worse survival outcomes (1–3, 5–7) compared with non-Hispanic white patients. Despite recent improvements in breast cancer survival overall (8, 9), these racial/ethnic disparities persist and have even widened somewhat for patients with more advanced stage diseases (10–14).

There is also evidence that African Americans and Hispanics are at a higher risk of more aggressive subtypes of breast cancer (15, 16). Breast cancer subtypes defined jointly by hormone receptor (HR) and HER2 status have distinct disease trajectories and treatment regimens (17). However, results across studies that have assessed known disparities according to breast cancer subtypes have been mixed. While some studies found no difference in survival outcomes between African American and white women with triple-negative breast cancer (18, 19), other studies suggest that African Americans still fare a higher breast cancer mortality after accounting for ER/PR/HER2 subtypes (5, 20–22). With respect to other race/ethnicities, California-based studies have found Asian/Pacific Islanders were more likely to be diagnosed with HER2$^+$ breast cancer, but patterns of late diagnosis by breast cancer subtypes varied by subgroups within Asian/Pacific Islanders (23–25). These prior studies were generally based on data from a single medical institution or from a particular geographic region. The population-based Surveillance, Epidemiology, and End Results (SEER) program of the NCI began collecting HER2 information for all breast cancer cases diagnosed in 2010 (26), enabling the assessment of these disparities on a much larger population-based scale. The goal of this study is to utilize these newly available data to characterize racial/ethnic differences in cancer stages and treatment patterns across breast cancer subtypes using a nationally representative sample. Later stage of diagnosis and receipt of non–guideline-concordant treatment, key factors influencing breast cancer survival, have been associated with limited access to health care, lower use of screening mammograms or a longer follow-up time after abnormal screenings, and broader social economic contextual factors (27–29). Disparities in breast cancer survival could not be directly assessed in this study due to the short follow-up time for these recent breast cancer cases in SEER data (only 2-year follow-up was available for cases diagnosed in 2010–2011 at the time of analysis of this study).

Materials and Methods

Women aged 20 years or older diagnosed with a primary invasive breast cancer between January 2010 and December 2011 were identified through 18 U.S. population-based cancer registries participating in the SEER program. These 18 cancer registries included in the study serve state or areas of San-Francisco-Oakland, Connecticut, Detroit, Hawaii, Iowa, New

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Mexico, Seattle, Utah, Atlanta, Alaska Natives, San Jose-Monterey, Los Angeles, rural Georgia, California, Kentucky, Louisiana, New Jersey, and greater Georgia, encompassing an estimated 28% of the total U.S. population (30). Among a total of 118,558 breast cancer cases identified, women were excluded in a stepwise fashion if they had unknown HER2 or HR status ($n = 13,114$), unknown AJCC stage of cancer ($n = 2,637$), or unknown race/ethnicity ($n = 743$) leaving a final analysis sample consisting of 102,064 breast cancer cases.

All study data were obtained from the publicly available SEER database using SEER*Stat 8.1.2 (NCI, Bethesda, MD), including demographic characteristics, breast cancer subtypes (HR/HER2), AJCC stage (7th edition), tumor grade, tumor size, primary treatment (primary surgery and radiotherapy), and health insurance status. Trained coders at SEER registries routinely collect data on these variables from hospital medical records and pathology reports. All analyses were stratified by breast cancer subtypes defined jointly by HR and HER2 receptor status. Details on this SEER-derived variable have been described previously (15). Briefly, HER2 information was coded by the SEER program using either summary results collected and submitted by individual cancer registries, or a validated algorithm combining existing SEER site-specific variables that contain HER2 testing results. The latter was done for 7% of all breast cancer cases who did not have HER2 summary information (26). The SEER program recoded data on ER, PR, and HER2 status according to the collaborative stage data collection system and created four categories based on combinations of these three variables: $HR^+/HER2^-$, $HR^-/HER2^-$ (triple negative), $HR^+/HER2^+$, and $HR^-/HER2^+$ (31). HR^+ tumors were those that were ER^+ and/or PR^+ and HR^- tumors were those that were ER^- and PR^-. Our analyses of primary treatment were restricted to women <70 years of age with stage I/II disease and tumors <2.0 cm because according to the National Comprehensive Cancer Network Clinical Practice Guidelines for breast cancer (32) the same primary treatment is recommended for all women meeting these criteria regardless of their ER, PR, and HER2 status. Women whose primary treatment regimen was unknown were dropped for these analyses. Primary treatments that were considered guideline concordant included either receipt of a total mastectomy or a breast conserving surgery (BCS) with radiotherapy. Evidence from large randomized clinical trials have confirmed that a mastectomy or a BCS plus radiation are equivalent in lowering the risk of breast cancer recurrence and mortality (33), superior to BCS without radiation, which increases risks for breast cancer recurrence and death (34). Women were classified as receiving a total mastectomy if they were coded as having had a total (simple) mastectomy, modified radical mastectomy, radical mastectomy, extended radical mastectomy, or bilateral mastectomy. Although bilateral mastectomy is not routinely recommended to women with breast cancer in general due to its aggressive nature and uncertainty regarding its effect on overall survival benefit, 1,285 women (3% of the analytic sample for analysis on treatment) who underwent this procedure were coded as having had complete first course treatment (35). Women were classified as having breast conserving surgery if they were coded as having had a partial (less than total) mastectomy (which includes partial mastectomy with nipple resection, lumpectomy or excisional biopsy, reexcision of the biopsy site, segmental mastectomy and partial mastectomy, NOS) or a subcutaneous mastectomy. Patients receiving beam radiation, radioactive implants, combined radiotherapy, or radiation, NOS, were classified as having received radiotherapy. Use of radiotherapy as a first course treatment recorded in SEER has a 94% agreement with that determined from claims data (36). The 50 patients who received only radioisotopes for their radiation treatment were excluded from these treatment analyses.

Polytomous logistic regression was used to calculate OR and their associated 95% confidence intervals (CI) for the associations between race/ethnicity (categorized as non-Hispanic white, African American, Hispanic white, Asian/Pacific Islander, and American Indian/Alaska Native; Hispanic blacks were excluded from this analysis due to the small sample size) and (i) cancer stage at diagnosis, and (ii) receipt of guideline-concordant treatment for stage I/II patients, stratified by breast cancer subtypes. We further explored heterogeneity of these associations among subgroups of Asian/Pacific Islanders, including Chinese, Japanese, Filipinos, Pacific Islanders, and others. In all analyses non-Hispanic white patients served as the comparison group. Consistent with prior studies (1, 3, 16, 37, 38), stage I and receiving guideline-concordant treatment were the referent categories for analyses of cancer stage and receipt of primary treatment, respectively. Stage III and stage IV were collapsed due to rarity of cases for analyses among Asian subgroups. Potential confounders were assessed (as listed and categorized in Table 1 with unknowns treated as a separate category whenever appropriate) and those that changed the risk estimates by more than 10% were included in final regression models. Thus, analyses of cancer stage were adjusted for age at diagnosis, marital status, health insurance status, and breast cancer subtypes (the latter for the overall analysis only). Analyses of the receipt of guideline-concordant treatment were adjusted for age, stage, and breast cancer subtypes (the latter for the overall analysis only). Health insurance status was assessed as an effect modifier in the associations between race/ethnicity and cancer stage or receipt of guideline-concordant treatment using the log likelihood ratio test. Tests on interactions were only performed for breast cancer overall but not for each breast cancer subtype due to limited power. The interaction was only statistically significant for associations between race/ethnicity and cancer stage and thus further stratification by insurance status was conducted.

Results

Non-Hispanic white women were somewhat older, more likely to be insured, and more likely to have $HR^+/HER2^-$, smaller tumors compared with women in each of the other racial/ethnic groups (Table 1). Compared with all other groups, African American women were somewhat more likely to be single and to have triple negative and larger tumors. Hispanic white women were somewhat more likely to be younger than 50 years and to be uninsured. Asian/Pacific Islander women were somewhat more likely to be married and to have $HR^-/HER2^+$ tumors compared with women in the other groups. Finally, American Indian/Alaska Native women were more likely to have $HR^+/HER2^+$ breast cancer and to receive Medicaid.

Compared with non-Hispanic whites, women of all other racial/ethnic groups had 20% to 60% higher risks of stage II–IV breast cancer overall (Table 2). According to HR/HER2 subtypes, African American women had 30% to 70% higher risks of stage II–IV $HR^+/HER2^-$ and triple-negative tumors, and a 40% higher risk of stage IV $HR^+/HER2^+$ and $HR^-/HER2^+$ breast cancers. Hispanic whites were 30% to 40% more likely to be diagnosed at stage II across all breast cancer subtypes, and 30% to 40% more likely to have stage III $HR^+/HER2^-$ and $HR^+/HER2^+$ cancers.

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Table 1. Selected characteristics of women diagnosed with invasive breast cancer between 2010–2011, by race/ethnicity[a]

	Non-Hispanic white *n* = 72,623 *n* (%)	African American *n* = 10,874 *n* (%)	Hispanic white *n* = 9,944 *n* (%)	Asian/Pacific Islander *n* = 8,068 *n* (%)	American Indian/ Alaska Native *n* = 555 *n* (%)
Age					
20–49	12,784 (17.6)	2,923 (26.9)	3,277 (33.0)	2,340 (29.0)	146 (26.3)
50–64	27,120 (37.3)	4,392 (40.4)	3,850 (38.7)	3,336 (41.3)	239 (43.1)
65–74	17,396 (24.0)	2,151 (19.8)	1,690 (17.0)	1,449 (18.0)	112 (20.2)
75+	15,323 (21.1)	1,408 (12.9)	1,127 (11.3)	943 (11.7)	58 (10.5)
Marital status					
Single	8,239 (11.3)	3,201 (29.4)	1,814 (18.2)	1,068 (13.2)	104 (18.7)
Married	40,831 (56.2)	3,686 (33.9)	5,359 (53.9)	5,167 (64.0)	245 (44.1)
Separated/divorced/unmarried	8,408 (11.6)	1,790 (16.5)	1,265 (12.7)	615 (7.6)	67 (12.1)
Widowed	11,460 (15.8)	1,540 (14.2)	994 (10.0)	870 (10.8)	62 (11.2)
Unknown	3,685 (5.1)	657 (6.0)	512 (5.1)	348 (4.3)	77 (13.9)
Health insurance status					
Insured	65,345 (90.0)	8,128 (74.7)	6,967 (70.1)	6,663 (82.6)	321 (57.8)
Any Medicaid	5,200 (7.2)	2,257 (20.8)	2,475 (24.9)	1,120 (13.9)	203 (36.6)
Uninsured	850 (1.2)	339 (3.1)	380 (3.8)	155 (1.9)	5 (0.9)
Unknown	1,228 (1.7)	150 (1.4)	122 (1.2)	130 (1.6)	26 (4.7)
Breast cancer subtypes					
$HR^+/HER2^-$	55,179 (76.0)	6,605 (60.7)	6,830 (68.7)	5,792 (71.8)	396 (71.4)
Triple negative	7,745 (10.7)	2,458 (22.6)	1,395 (14.0)	784 (9.7)	66 (11.9)
$HR^+/HER2^+$	6,842 (9.4)	1,190 (10.9)	1,155 (11.6)	962 (11.9)	67 (12.1)
$HR^-/HER2^+$	2,857 (3.9)	621 (5.7)	564 (5.7)	530 (6.6)	26 (4.7)
Tumor size					
<2 cm	42,842 (59.0)	5,047 (46.4)	4,798 (48.3)	4,239 (52.5)	280 (50.5)
2–4.9 cm	22,991 (31.7)	4,140 (38.1)	3,908 (39.3)	2,988 (37.0)	200 (36.0)
≥5 cm	5,919 (8.2)	1,452 (13.4)	1,111 (11.2)	748 (9.3)	67 (12.1)
Unknown	871 (1.2)	235 (2.2)	127 (1.3)	93 (1.2)	8 (1.4)

[a]Variables were analyzed as categorized in the table and unknowns were treated as separate categories whenever appropriate.

A 10% to 30% higher risk of stage II tumors was seen for Asian/Pacific islander women across all subtypes except $HR^-/HER2^+$. American Indian/Alaska Native women had 2.0- to 3.9-fold higher risks of stage II–IV triple-negative breast cancer in addition to a 1.6-fold higher risk of stage III $HR^+/HER2^-$ disease. Risk for a late diagnosis differed within Asian/Pacific Islanders as Filipinos and Pacific Islanders had 20% to 60% higher risks of stage III/IV breast cancer while Chinese and Japanese women had 30% to 40% lower risks compared with non-Hispanic white women (Table 3). Suggestive elevations in risk of stage II–IV cancers were observed for Filipino and Pacific Islander women for all breast cancer subtypes except $HR^-/HER2^+$, although some risk estimates were not statistically significant. In contrast, Chinese women had 1.5-fold increased risk of stage II $HR^+/HER2^+$ cancers and Japanese women had 2.7-fold increased risk of stage II $HR^-/HER2^+$ cancers. When the association between cancer stage and race/ethnicity was stratified by insurance status for breast cancer overall, similar patterns were observed with the magnitude of associations being greatest among the uninsured and those whose insurance status were unknown (data not shown).

The majority (≥79%) of women with stage I/II tumors less than 2.0 cm in size (n = 37,053) received guideline-concordant primary treatment regardless of race/ethnicity or breast cancer subtypes (Table 4). Combining all breast cancer subtypes, African American and Hispanic white patients were 30% to 40% more likely to receive non guideline-concordant primary treatment compared with non-Hispanic white women, while no significant differences in treatment patterns were seen for Asian/Pacific Islander and American Indian/Alaska Native women. Notably, African American women had a consistent 30% to 60% higher risk of receiving non–guideline-concordant treatment across all breast cancer subtypes except $HR^-/HER2^+$. Similarly, a 20% to 40% higher risk of receiving non–guideline-concordant treatment was also observed for Hispanic white patients for all but $HR^-/HER2^+$ and triple-negative cancers. In contrast, Asian/Pacific Islander patients appeared to be no different from non-Hispanic white patients in receiving appropriate primary treatment across all subtypes and that holds for major ethnicities within Asian/Pacific Islanders (data not shown). American Indian/Alaska Native women had 20% to 50% higher risks of receiving inappropriate treatment across all subtypes, but all of these risk estimates were within the limits of chance. A sensitivity analysis excluding the women who received a bilateral mastectomy from our treatment analysis study sample demonstrated that this exclusion did not change our results.

Discussion

Consistent with the literature, our study found that African American (1–3, 39), Hispanic white (1–3, 40), Asian/Pacific Islander (1, 3), and American Indian/Alaska Native (1, 3, 41, 42) women had elevated risks of being diagnosed with more advanced stages of breast cancer compared with non-Hispanic white women. As reported by previous studies, African American (1, 3, 43–45) and Hispanic white (1, 3, 45) patients with early-stage breast cancer were also more likely to receive inappropriate primary treatment following breast cancer diagnoses. Beyond confirming these results, we further characterized racial/ethnic disparities within each molecular subtype of breast cancer and observed some variability across breast cancer subtypes. Notably, African Americans had elevated risks of both late diagnosis and receipt of non–guideline-concordant primary treatment across all

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Table 2. Cancer stage at diagnosis and race/ethnicity by breast cancer subtypes

	Non-Hispanic white $n = 72,623$	African American $n = 10,874$		Hispanic white $n = 9,944$		Asian/Pacific Islander $n = 8,068$		American Indian/ Alaska Native $n = 555$	
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Stages, all subtypes[a]									
I	39,179 (53.9)	4,318 (39.7)	1.0 (Ref)	4,216 (42.4)	1.0 (Ref)	3,937 (48.8)	1.0 (Ref)	237 (42.7)	1.0 (Ref)
II	22,195 (30.6)	3,986 (36.7)	**1.3 (1.3–1.4)**	3,696 (37.2)	**1.3 (1.2–1.4)**	2,856 (35.4)	**1.2 (1.1–1.2)**	189 (34.1)	1.2 (1.0–1.5)
III	7,796 (10.7)	1,700 (15.6)	**1.5 (1.4–1.5)**	1,486 (14.9)	**1.3 (1.2–1.4)**	921 (11.4)	1.0 (0.9–1.1)	95 (17.1)	**1.5 (1.2–1.9)**
IV	3,453 (4.8)	870 (8.0)	**1.6 (1.4–1.7)**	546 (5.5)	1.1 (1.0–1.2)	354 (4.4)	0.9 (0.8–1.0)	34 (6.1)	1.1 (0.7–1.6)
$HR^+/HER2^-$[b]									
I	32,036 (58.1)	2,973 (45.0)	1.0 (Ref)	3,274 (47.9)	1.0 (Ref)	3,103 (53.6)	1.0 (Ref)	191 (48.2)	1.0 (Ref)
II	15,838 (28.7)	2,239 (33.9)	**1.4 (1.3–1.5)**	2,348 (34.4)	**1.3 (1.2–1.3)**	1,904 (32.9)	**1.1 (1.1–1.2)**	124 (31.3)	1.1 (0.9–1.4)
III	5,074 (9.2)	937 (14.2)	**1.6 (1.5–1.8)**	895 (13.1)	**1.3 (1.2–1.5)**	563 (9.7)	1.0 (0.9–1.1)	63 (15.9)	**1.6 (1.2–2.1)**
IV	2,231 (4.0)	456 (6.9)	**1.7 (1.5–1.9)**	313 (4.6)	1.0 (0.9–1.2)	222 (3.8)	0.9 (0.8–1.1)	18 (4.5)	0.9 (0.5–1.5)
Triple negative[b]									
I	3,130 (40.4)	741 (30.1)	1.0 (Ref)	412 (29.5)	1.0 (Ref)	274 (34.9)	1.0 (Ref)	13 (19.7)	1.0 (Ref)
II	3,021 (39.0)	1,089 (44.3)	**1.3 (1.2–1.5)**	678 (48.6)	**1.4 (1.2–1.6)**	349 (44.5)	**1.2 (1.0–1.5)**	29 (43.9)	**2.0 (1.0–3.9)**
III	1,143 (14.8)	432 (17.6)	**1.3 (1.1–1.5)**	230 (16.5)	1.2 (1.0–1.4)	112 (14.3)	1.0 (0.8–1.3)	14 (21.2)	**2.4 (1.1–5.2)**
IV	451 (5.8)	196 (8.0)	**1.4 (1.1–1.7)**	75 (5.4)	0.9 (0.7–1.2)	49 (6.3)	1.2 (0.8–1.6)	10 (15.2)	**3.9 (1.7–9.2)**
$HR^+/HER2^+$[b]									
I	2,951 (43.1)	419 (35.2)	1.0 (Ref)	374 (32.4)	1.0 (Ref)	374 (38.9)	1.0 (Ref)	27 (40.3)	1.0 (Ref)
II	2,389 (34.9)	436 (36.6)	1.2 (1.0–1.3)	455 (39.4)	**1.3 (1.1–1.5)**	403 (41.9)	**1.3 (1.1–1.5)**	24 (35.8)	0.9 (0.5–1.6)
III	1,000 (14.6)	201 (16.9)	1.2 (1.0–1.4)	228 (19.7)	**1.4 (1.2–1.7)**	136 (14.1)	1.0 (0.8–1.2)	11 (16.4)	0.9 (0.4–1.8)
IV	502 (7.3)	134 (11.3)	**1.4 (1.1–1.8)**	98 (8.5)	1.2 (0.9–1.5)	49 (5.1)	0.7 (0.5–1.0)	5 (7.5)	0.7 (0.3–2.0)
$HR^-/HER2^+$[b]									
I	1,062 (37.2)	185 (29.8)	1.0 (Ref)	156 (27.7)	1.0 (Ref)	186 (35.1)	1.0 (Ref)	6 (23.1)	1.0 (Ref)
II	947 (33.1)	222 (35.7)	1.2 (0.9–1.5)	215 (38.1)	**1.3 (1.1–1.7)**	200 (37.7)	1.2 (0.9–1.5)	12 (46.2)	2.0 (0.7–5.4)
III	579 (20.3)	130 (20.9)	1.0 (0.8–1.3)	133 (23.6)	1.2 (0.9–1.5)	110 (20.8)	1.0 (0.8–1.3)	7 (26.9)	1.7 (0.6–5.2)
IV	269 (9.4)	84 (13.5)	**1.4 (1.0–1.9)**	60 (10.6)	1.2 (0.8–1.7)	34 (6.4)	0.7 (0.5–1.0)	1 (3.8)	0.5 (0.1–4.5)

[a]ORs were adjusted for age groups, breast cancer subtypes, marital status, and health insurance status.
[b]ORs were adjusted for age groups, marital status, and health insurance status. ORs are in bold if *P* values are <0.05.

subtypes. For triple-negative breast cancer in particular, the most aggressive subtype of the disease (17), African American women had 30% to 40% higher risk of being diagnosed at stage II–IV and 60% more likely to receive inappropriate treatment compared with non-Hispanic white women. These differences in stage distribution and cancer treatment may explain the poorer survival outcomes experienced by African American women with triple-negative breast cancer observed in prior studies (5, 20). While the higher incidence rates of triple-negative breast cancer observed among African American women are likely to be driven by differences in risk factor distributions and biology (46, 47), the elevated risks of late-stage disease and receipt of less optimal treatment observed for African American women regardless of tumor subtypes suggest that factors related to socioeconomic

Table 3. Cancer stage at diagnosis and Asian subgroups by breast cancer subtypes

	Non-Hispanic white $n = 72,623$	Chinese $n = 1,431$		Japanese $n = 1,058$		Filipinos $n = 1,960$		Pacific Islanders $n = 515$		Others $n = 3,104$	
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Stages, all subtypes[a]											
I	39,179 (53.9)	746 (52.1)	1.0 (Ref)	630 (59.5)	1.0 (Ref)	872 (44.5)	1.0 (Ref)	221 (42.9)	1.0 (Ref)	1,468 (47.3)	1.0 (Ref)
II	22,195 (30.6)	498 (34.8)	1.1 (0.9–1.2)	325 (30.7)	0.9 (0.8–1.0)	734 (37.4)	**1.4 (1.2–1.5)**	186 (36.1)	**1.4 (1.2–1.8)**	1,113 (35.9)	**1.2 (1.1–1.3)**
III/IV	11,249 (15.5)	187 (13.1)	**0.7 (0.6–0.9)**	103 (9.7)	**0.6 (0.5–0.7)**	354 (18.1)	**1.2 (1.1–1.4)**	108 (21.0)	**1.6 (1.2–2.0)**	523 (16.8)	1.0 (0.9–1.1)
$HR^+/HER2^-$[b]											
I	32,036 (58.1)	578 (57.2)	1.0 (Ref)	529 (64.4)	1.0 (Ref)	669 (48.2)	1.0 (Ref)	186 (46.7)	1.0 (Ref)	1,141 (52.4)	1.0 (Ref)
II	15,838 (28.7)	320 (31.7)	1.0 (0.9–1.2)	226 (27.5)	**0.9 (0.7–1.0)**	500 (36.0)	**1.4 (1.3–1.6)**	140 (35.2)	**1.4 (1.2–1.8)**	718 (33.0)	**1.1 (1.0–1.2)**
III/IV	7,305 (13.2)	113 (11.2)	**0.7 (0.6–0.9)**	66 (8.0)	**0.6 (0.4–0.7)**	218 (15.7)	**1.3 (1.1–1.5)**	72 (18.1)	**1.5 (1.2–2.0)**	316 (14.5)	1.0 (0.9–1.1)
Triple negative[b]											
I	3,130 (40.4)	63 (41.4)	1.0 (Ref)	47 (38.2)	1.0 (Ref)	47 (32.0)	1.0 (Ref)	10 (27.8)	1.0 (Ref)	107 (32.8)	1.0 (Ref)
II	3,021 (39.0)	65 (42.8)	1.0 (0.7–1.4)	59 (48.0)	1.4 (0.9–2.1)	61 (41.5)	1.3 (0.8–1.8)	16 (44.4)	1.5 (0.7–3.3)	148 (45.4)	1.3 (1.0–1.6)
III/IV	1,594 (20.6)	24 (15.8)	0.7 (0.4–1.2)	17 (13.8)	0.7 (0.4–1.3)	39 (26.5)	1.5 (1.0–2.3)	10 (27.8)	1.8 (0.7–4.3)	71 (21.8)	1.2 (0.9–1.6)
$HR^+/HER2^+$[b]											
I	2,951 (43.1)	59 (38.8)	1.0 (Ref)	46 (56.8)	1.0 (Ref)	95 (33.2)	1.0 (Ref)	18 (31.6)	1.0 (Ref)	156 (40.4)	1.0 (Ref)
II	2,389 (34.9)	71 (46.7)	**1.5 (1.0–2.1)**	22 (27.2)	0.6 (0.4–1.0)	127 (44.4)	**1.6 (1.2–2.1)**	23 (40.4)	1.6 (0.8–2.9)	160 (41.5)	1.1 (0.9–1.4)
III/IV	1,502 (22.0)	22 (14.5)	0.7 (0.4–1.2)	13 (16.0)	0.6 (0.3–1.1)	64 (22.4)	1.2 (0.9–1.7)	16 (28.1)	1.7 (0.8–3.3)	70 (18.1)	0.8 (0.6–1.1)
$HR^-/HER2^+$[b]											
I	1,062 (37.2)	46 (39.7)	1.0 (Ref)	8 (24.2)	1.0 (Ref)	61 (43.6)	1.0 (Ref)	7 (29.2)	1.0 (Ref)	64 (29.5)	1.0 (Ref)
II	947 (33.2)	42 (36.2)	1.0 (0.6–1.5)	18 (54.5)	**2.7 (1.2–6.2)**	46 (32.9)	0.9 (0.6–1.3)	7 (29.2)	1.0 (0.3–2.8)	87 (40.1)	**1.4 (1.0–2.0)**
III/IV	848 (29.7)	28 (24.1)	0.7 (0.4–1.1)	7 (21.2)	1.3 (0.4–3.5)	33 (23.6)	0.7 (0.5–1.1)	10 (41.7)	1.5 (0.6–4.2)	66 (30.4)	1.1 (0.8–1.6)

[a]ORs were adjusted for age groups, breast cancer subtypes, marital status, and health insurance status.
[b]ORs were adjusted for age groups, marital status, and health insurance status. ORs are in bold if *P* values are <0.05.

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Table 4. Guideline concordant primary treatment and race/ethnicity by breast cancer subtypes

	Non-Hispanic white $n = 26,980$	African American $n = 3,380$		Hispanic white $n = 3,428$		Asian/Pacific Islander $n = 3,066$		American Indian/Alaska Native $n = 199$	
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
All subtypes[a]									
Concordant	23,538 (87.2)	2,774 (82.1)	Ref	2,882 (84.1)	Ref	2,691 (87.8)	Ref	168 (84.4)	Ref
Nonconcordant	3,442 (12.8)	606 (17.9)	**1.4 (1.3–1.6)**	546 (15.9)	**1.3 (1.2–1.4)**	375 (12.2)	1.0 (0.9–1.1)	31 (15.6)	1.3 (0.9–1.9)
$HR^+/HER2^-$[b]									
Concordant	18,994 (88.1)	1,926 (84.4)	Ref	2,220 (85.4)	Ref	2,104 (88.5)	Ref	140 (84.3)	Ref
Nonconcordant	2,577 (11.9)	357 (15.6)	**1.3 (1.2–1.5)**	380 (14.6)	**1.3 (1.1–1.4)**	275 (11.5)	1.0 (0.8–1.1)	26 (15.7)	1.3 (0.9–2.1)
Triple negative[b]									
Concordant	1,862 (83.2)	447 (75.1)	Ref	282 (80.6)	Ref	174 (86.6)	Ref	7 (77.8)	Ref
Nonconcordant	376 (16.8)	148 (24.9)	**1.6 (1.3–2.0)**	68 (19.4)	1.2 (0.9–1.6)	27 (13.4)	0.8 (0.5–1.2)	2 (22.2)	1.5 (0.3–7.1)
$HR^+/HER2^+$[b]									
Concordant	1,951 (84.3)	277 (79.6)	Ref	269 (79.1)	Ref	268 (83.0)	Ref	14 (82.4)	Ref
Nonconcordant	363 (15.7)	71 (20.4)	**1.4 (1.0–1.8)**	71 (20.9)	**1.4 (1.1–1.9)**	55 (17.0)	1.1 (0.8–1.5)	3 (17.6)	1.2 (0.3–4.1)
$HR^-/HER2^+$[b]									
Concordant	731 (85.3)	124 (80.5)	Ref	111 (80.4)	Ref	145 (89.0)	Ref	7 (100.0)	NA
Nonconcordant	126 (14.7)	30 (19.5)	1.4 (0.9–2.2)	27 (19.6)	1.5 (0.9–2.4)	18 (11.0)	0.7 (0.4–1.2)	0 (0.0)	

[a]ORs adjusted for age groups, stage (I vs. II), and breast cancer subtypes.
[b]ORs adjusted for age and stage (I vs. II). ORs are in bold if *P* values are <0.05.

factors and access to care are likely key drivers of these long-standing disparities that have been well characterized (21, 48, 49).

Similar disparities in stage at diagnosis were seen for Hispanic white, Filipino, and Pacific Islander women compared with non-Hispanic white counterparts across most breast cancer subtypes consistent with prior studies (1–3). Disparities in treatment were also consistently observed across breast cancer subtypes among Hispanic white women. Although it is increasingly recognized that Hispanic women are also more likely to be diagnosed with breast cancer subtypes that have less favorable outcomes such as triple negative and $HR^-/HER2^+$ tumors (15, 50), our study is the first to report on subtype specific risks of late stage diagnosis and receipt of inappropriate treatment. This again suggests that social, cultural, and economic factors are likely the primary contributors to these disparities. Hispanic women in our sample were more likely to be uninsured than any other racial/ethnic group, and lack of insurance and/or access to care was suggested to be the strongest predictor for low breast cancer screening adherence among Hispanic women (51–53). However, the disparities observed here did persist after adjusting for health insurance status, suggesting that other factors also play important roles.

Beyond confirming that American Indian/Alaska Native are more likely to be diagnosed with more advanced stage breast cancer overall (1, 3, 41, 42), we found this risk was confined primarily to triple-negative disease. According to a 2010 national survey, American Indian/Alaska Native reported the lowest breast cancer screening rate of all women aged 40 years or older, 63.9% compared with 75.4% among non-Hispanic whites (54). Another study involving American Indian/Alaska Native women in the Northern Plains found that the screening rate was lowest among 41–49 age group, with a rate as low as 33% (41). This missed opportunity in breast cancer screening among American Indian/Alaska Native may have contributed to the risk of late diagnosis of breast cancer overall, but it is not clear why the elevated risk was only seen for the triple-negative subtype. While a recent study found American Indian/Alaska Native women were less likely to receive guideline-concordant breast cancer care (55), none of the risk estimates in our study across breast cancer subtypes was statistically significant. However, this could be due to the small sample size in this subset of patients in our sample as there was some suggestion for such associations across breast cancer subtypes in our data based on the point estimates.

It is important to acknowledge the limitations of this study. We excluded 11% of women in the original sample who were missing data on HR and/or HER2 status (total exclusion 14% due to missing in stage, race/ethnicity in addition to HR/HER2 status) and this missingness has been shown to correlate with particular patient characteristics and cancer registries (15). Furthermore, there is some variation in the reporting, testing, and interpretation of these tumor biomarkers between hospitals both within and across the 18 cancer registries. It is not clear to what extent the bias introduced by non-random missing data and/or variation in the reporting of HR/HER2 status would change our results, particularly for the less common breast cancer subtypes with smaller sample sizes. There is also potential for misclassification of race/ethnicity given that these data are abstracted from medical records. We focused on the receipt of primary breast cancer treatment and were not able to assess other aspects of breast cancer care due to the lack of data on chemotherapy, hormonal therapy, and trastuzumab use in SEER. However, disparities related to these treatments have been reported in other studies with similar patterns observed by race/ethnicity (56, 57). In addition, patients' health insurance status was determined from medical records. We did conduct a sensitivity analysis restricted to women younger than 65 years (given that those aged 65 or above are Medicare eligible), and our results remained largely unchanged. Finally, we did not have data on individual level socioeconomic status, use of mammography screening, family history, or other lifestyle factors that may have contributed to the observed disparities. Future studies with detailed individual level data are needed to further characterize factors underlying the racial/ethnic patterns in breast cancer diagnosis and treatment and if these contributing factors vary by breast cancer subtypes.

In summary, our study shows disparities in late stage diagnosis and receipt of guideline-concordant primary treatment persist irrespective of breast cancer subtypes for African American, Hispanic white, Filipina, and Pacific Islander women, but that the higher risk of advanced stage breast cancer observed among American Indians/Alaska Natives may be largely confined to triple-negative disease. As contributors to racial/ethnic disparities in breast cancer are complex and multifactorial, continued efforts,

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especially targeted, culturally appropriate interventions, to address these disparities across different subtypes of breast cancer have the potential to reduce these long-standing disparities and hopefully close the existing survival gaps.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Conception and design: L. Chen, C.I. Li
Development of methodology: L. Chen, C.I. Li
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Chen, C.I. Li
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Chen, C.I. Li
Writing, review, and/or revision of the manuscript: L. Chen, C.I. Li
Study supervision: C.I. Li

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Racial Disparities in Breast Cancer Diagnosis and Treatment by Hormone Receptor and HER2 Status

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