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Article

ARTICLE

Racial Disparities in Breast Cancer Outcomes in the Metropolitan Atlanta Area: New Insights and Approaches for Health Equity

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Abstract

Background: Racial disparities in breast cancer (BC) outcomes persist where non-Hispanic black (NHB) women are more likely to die from BC than non-Hispanic white (NHW) women, and the extent of this disparity varies geographically. We evaluated tumor, treatment, and patient characteristics that contribute to racial differences in BC mortality in Atlanta, Georgia, where the disparity was previously characterized as especially large.
Methods: We identified 4943 NHW and 3580 NHB women in the Georgia Cancer Registry with stage I–IV BC diagnoses in Atlanta (2010–2014). We used Cox proportional hazard regression to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) comparing NHB vs NHW BC mortality by tumor, treatment, and patient characteristics on the additive and multiplicative scales. We additionally estimated the mediating effects of these characteristics on the association between race and BC mortality.
Results: At diagnosis, NHB women were younger—with higher stage, node-positive, and triple-negative tumors relative to NHW women. In age-adjusted models, NHB women with luminal A disease had a 2.43 times higher rate of BC mortality compared to their NHW counterparts (95% CI = 1.99 to 2.97). High socioeconomic status (SES) NHB women had more than twice the mortality rates than their white counterparts (HR = 2.67, 95% CI = 1.65 to 4.33). Racial disparities among women without insurance, in the lowest SES index, or diagnosed with triple-negative BC were less pronounced.
Conclusions: In Atlanta, the largest racial disparities are observed in luminal tumors and most pronounced among women of high SES. More research is needed to understand drivers of disparities within these treatable features.

Breast cancer (BC) prognosis has dramatically improved in recent decades (1,2), in part because of the introduction of biomarker-driven therapies (2–6). Yet, non-Hispanic black (NHB) women experience a disproportionate burden of poor BC outcomes and are more likely to die from BC than women of any other race or ethnicity (7). Racial disparities in BC-specific mortality vary geographically and are most pronounced in the southeastern region (8). A recent study, conducted using resources from the 500 Cities project, reported that race mortality disparities in Atlanta, Georgia, not only were among the largest in the United States but also had widened between 2005 and 2014 (9), despite national and local efforts to reduce the mortality gap. Although the reported widening disparity is likely an overestimation (due to the small sample size,

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open cohort design, and an ill-defined source population), with improvements in cancer care, it is increasingly imperative to understand the factors that drive disparate BC outcomes (10–14).

The available evidence suggests that prognostic disparities are related to a complex combination of biologic (15–17), treatment (18), and patient-level factors (19) that manifest during both the pre- and post-diagnostic periods (20). Previous investigations have limitedly addressed causal drivers of disparities in single-center studies with small samples, socioeconomically homogenous cohorts, and short or incomplete follow-up. These constraints impede the ability to describe the magnitude of disparities within strata of important factors. More robust population-based studies are needed to examine these complex relationships.

Atlanta represents an ideal setting to evaluate factors contributing to racial disparities in BC-specific mortality. It is a large metropolitan city of nearly 4 million inhabitants with diverse population demographics. According to the 2010 US Census, 32% of the population identified as NHB and 61% as non-Hispanic white (NHW), nearly 27% of Atlanta residents had an income below the poverty level, and 15% lacked health insurance (21). Thus, the primary aims of this study were to assess the tumor, treatment, and patient characteristics that contribute to differences in BC-specific mortality between NHB and NHW women diagnosed with a first primary stage I–IV BC in the metropolitan Atlanta area.

Methods

Study Population

The Georgia Cancer Registry (GCR) is a statewide population-based registry that has collected all cancer cases diagnosed among Georgia residents since January 1, 1995. Using this registry, we identified NHB and NHW women with a first primary stage I–IV BC diagnosis (*International Classification of Diseases* [ICD]-O-3- C50) occurring between January 1, 2010, and December 31, 2014. Women were included if they resided in the metropolitan Atlanta area at the time of diagnosis. All other diagnoses were excluded, including those among other race and/or ethnic groups, patients younger than 18 years, male patients, patients with a previous history of cancer or any secondary tumor diagnoses, and patients with in situ disease. In addition, patients were excluded if diagnosed solely by death certificate or if stage was missing in the registry.

Exposure Assessment

Race and ethnicity were obtained from documentation in medical records using classifications similar to the 2010 census. When medical record data were not available, Hispanic ethnicity was determined by the North American Association of Central Cancer Registries Hispanic Identification Algorithm (22), which uses a combination of variables routinely captured by registries (eg, birthplace, race, and names) in addition to Hispanic surname lists from the US Census to classify women as Hispanic or non-Hispanic.

Outcome Assessment

Underlying cause of death was determined directly from death certificates using ICD-10 codes. The GCR links to the Georgia vital statistics registry annually to identify deaths and causes of death from the preceding year. Additionally, the GCR also links to the US National Death Index each year to identify deaths that occur outside of Georgia. In this study, we included only BC-related deaths recorded through December 31, 2016, because linkage to vital records files were not complete for 2017 at the time the dataset was constructed.

Covariates of Interest

Tumor Characteristics. Tumor characteristics used in this analysis included cancer stage at diagnosis, tumor grade, expression of the estrogen receptor (ER), expression of the progesterone receptor (PR), and extrapolated molecular subtype. Cancer stage at diagnosis was based on the American Joint Committee on Cancer 7th edition staging manual using combined clinical and pathologic information (23). Tumor grade was categorized as 1, 2, or 3 and above with priority coding for Nottingham or Bloom-Richardson score grades. Hormone receptor expression was classified as positive or negative based on the expression of ER, PR, or both. HER2 expression was similarly classified as positive or negative and has been routinely collected by the GCR since 2010 (24). Molecular subtype was based on the joint expression of hormone receptor and HER2: luminal A (hormone receptor+/HER2−), luminal B (hormone receptor+/HER2+), HER2 overexpressing (hormone receptor−/HER2+), and triple-negative BC (TNBC) was a lack of expression of either tumor biomarker (25).

Treatment Characteristics. We considered different treatment modalities as possible contributors to mortality disparities. This included primary surgery (no surgery, breast conserving surgery, or mastectomy) and adjuvant therapy. Adjuvant therapies included receipt of chemotherapy (yes/no), radiation therapy (yes/no), hormone therapy (yes/no, among women diagnosed with ER+ disease), and trastuzumab (yes/no, among women diagnosed with HER2+ disease). In addition to the dates recording initiation of therapy, textual descriptions of the actual antineoplastic agents are captured by the GCR for most cases. Until 2013, HER2-targeted therapies were captured within the chemotherapy variable in GCR; therefore, these textual descriptions were algorithmically searched for each patient to identify records that suggested receipt of HER2-targeted therapy. Thus, patients with an annotation that indicated such therapy were assumed to have received the therapy and those without a corresponding annotation were assumed to not have received the adjuvant therapy.

Patient Characteristics. We considered different patient demographic characteristics at the time of diagnosis that may have contributed to disparate cancer outcomes. These included type of health insurance (uninsured, private, Medicaid, and Medicare), age at diagnosis (<40, 40–49, 50–65, >65 years), marital status (married, single, divorced, widowed, and/or separated), and socioeconomic status (SES) index for the neighborhood poverty level, based on the census tract of the patient's residence at diagnosis (0%–<5%, 5%–<10%, 10%–<20%, 20%–100%) (26). The tract-level poverty data are published annually from the American Community Survey (27) and have been used widely in population studies (28,29).

Statistical Methods

Descriptive statistics were calculated for covariates across each population subgroup as median values with a SD, or frequency

and proportion within categories. Follow-up was defined as time, in months, from the date of diagnosis until the first of 1) mortality event (due to BC or other cause of death), 2) last date of contact in the registry, or 3) December 31, 2016. Individuals were censored if their last date of contact was before the end of the study period or if they died from any cause unrelated to their BC. We used age-adjusted and multivariable-adjusted Cox proportional hazard models to calculate the hazard ratios (HR) and 95% confidence intervals (CIs) for the association between race and BC-specific mortality (30). We used ln-ln survival curves and an interaction term of each covariate with time to verify the proportional hazards assumption. All variables satisfied the proportional hazards assumption. Potential confounders were determined a priori, based on previous literature and graphical-based methods (31,32). Interaction describes differences in the effect of one exposure across strata of another exposure, which depends on the scale. In this analysis, we assessed additive and multiplicative interaction for the effect of race on BC mortality by patient, tumor, and treatment characteristics. To assess the presence of interaction between race and the characteristics of interest, we used the common referent approach to calculate the relative excess risk due to interaction (RERI), evaluating departure of the effect on the additive scale, indicating that the combined effect of the two exposures is greater than the sum of the individual effects (33). We used the delta method to calculate the corresponding 95% confidence interval using the variance-covariance matrix from the effect estimates (34). The presence of multiplicative interactions, indicating that the combined effect of the exposures is greater than the product of the individual effects, was assessed using the likelihood ratio test, with interaction terms included in the model and stratum-specific effect estimates reported.

Our graphical assessment of potential confounders showed that all covariates of interest were on the causal path between race and BC-specific mortality (Supplementary Figure 1, available online). Models were thus adjusted for age only. We additionally performed sensitivity analyses, adjusting for tumor and treatment characteristics. Because the covariates of interest were on the causal path, we used mediation techniques to evaluate the role of stage, subtype, and SES as intermediates on the path between race and BC-specific mortality (35), employing the multiple mediation analysis R package to account for the categorical mediators (36,37). Mediation techniques have been developed to quantify the direct and indirect effects of an exposure on an outcome through intermediates of interest. All analyses were carried out using R version 13.1 and SAS version 9.4 (Cary, NC).

Results

We identified 3580 NHB and 4943 NHW women diagnosed with a first primary BC between 2010 and 2014 in the metropolitan Atlanta area (Table 1). On average, women were followed for 3.5 years, range 0–7 years. We observed 488 BC-specific deaths among NHB women and 319 BC-specific deaths among NHW women. Compared to NHW BC patients, NHB women were more likely to be diagnosed at a younger age (<55 years: 46% vs 37%), with higher stage (stage IV: 9.4% vs 4.8%), grade (grade 3+: 45% vs 27%), node positive (33% vs 26%), and triple-negative tumors (18% vs 8.1%). NHB women were also more likely to receive neoadjuvant therapy (16% vs 9.9%) and chemotherapy (57% vs 40%). With respect to patient characteristics, NHB

Table 1. Patient demographic and clinicopathological characteristics among non-Hispanic white (NHW) and non-Hispanic black (NHB) women diagnosed with breast cancer in the metropolitan Atlanta area 2010–2014 and registered with the Georgia Cancer Registry

Characteristic	NHW (n = 4943)	NHB (n = 3580)
Age at diagnosis, median (SD), y	60 (13.3)	56 (13.0)
Length of follow-up, median (SD), months	44.6 (20.6)	42 (20.8)
Time to event, median (SD), months	23.33 (18.4)	20.87 (16.9)
Breast cancer-specific deaths, no. (%)	319 (6.5)	488 (14)
Age, no. (%), y		
<55	1807 (37)	1632 (46)
≥55	3136 (63)	1948 (54)
AJCC stage, no. (%)		
I	2727 (55)	1397 (39)
II	1537 (31)	1341 (37)
III	444 (9.0)	505 (14)
IV	235 (4.8)	337 (9.4)
Tumor grade, no. (%)		
1	1313 (27)	476 (13)
2	2052 (42)	1275 (36)
3+	1344 (27)	1608 (45)
Unknown	234 (4.7)	221 (6.2)
Tumor size, no. (%), cm		
≤0.5	564 (11)	305 (8.5)
0.6–1	869 (18)	427 (12)
>1 to <5	3085 (62)	2237 (62)
≥5	356 (7.2)	522 (15)
Unknown	69 (1.4)	89 (2.5)
Lymph node, no. (%)		
Node negative	3181 (64)	1899 (53)
Node positive	1307 (26)	1175 (33)
1–3	904 (18)	715 (20)
≥4	279 (5.6)	254 (7.1)
Unknown number	124 (2.5)	206 (5.8)
No nodes examined	450 (9.1)	494 (14)
Unknown node status	5 (0.1)	12 (0.4)
Estrogen receptor status, no. (%)		
ER− tumor	640 (13)	912 (25)
ER+ tumor	4248 (86)	2614 (73)
Unknown/Borderline	55 (1.1)	54 (1.5)
Molecular subtype, no. (%)		
HR+/HER2− (luminal A)	3511 (71)	2074 (58)
HR+/HER2+ (luminal B)	525 (11)	432 (12)
HR-/HER2+ (HER2 overexpressing)	172 (3.5)	185 (5.2)
HR-/HER2− (triple negative)	401 (8.1)	646 (18)
Unknown	334 (6.8)	243 (6.8)
Receipt of surgery, no. (%)		
Breast conserving surgery	2492 (50)	1600 (45)
Mastectomy	2105 (53)	1450 (41)
Unknown/None	346 (7.0)	530 (15)
Receipt of neoadjuvant therapy, no. (%)		
Yes	491 (9.9)	563 (16)
No	4452 (90)	3017 (84)
Receipt of chemotherapy, no. (%)		
Yes	1962 (40)	2035 (57)
No	2926 (59)	1483 (41)
Unknown	55 (1.1)	62 (1.7)
Receipt of radiation, no. (%)		
Yes	2805 (57)	2002 (56)
No	1974 (40)	1368 (38)
Unknown	164 (3.3)	210 (5.9)

(continued)

Table 1. (continued)

Characteristic	NHW (n = 4943)	NHB (n = 3580)
Receipt of hormone therapy (among ER+ tumors only),* no. (%)		
Yes	3426 (81)	2059 (79)
No	822 (19)	555 (21)
Receipt of trastuzumab (among HER2+ tumors only),* no. (%)		
Yes	481 (69)	445 (72)
No	216 (31)	172 (28)
Marital status, no. (%)		
Single	615 (12)	1109 (31)
Married (common law and unmarried domestic)	3025 (61)	1258 (35)
Divorced	547 (11)	596 (17)
Widowed	590 (12)	383 (11)
Separated	23 (0.5)	64 (1.8)
Unknown	143 (2.9)	170 (4.8)
SES index, no. (%)		
0–<5% poverty	1529 (31)	211 (5.9)
5–<10% poverty	1469 (30)	455 (13)
10–<20% poverty	1320 (26)	1297 (36)
20–100% poverty	625 (13)	1617 (45)
Insurance type, no. (%)		
Uninsured	57 (1.2)	144 (4.0)
Private	3101 (63)	1953 (55)
Medicaid	139 (2.8)	516 (14)
Medicare	1545 (31)	844 (24)
Military/Other†	39 (0.8)	65 (1.8)
Unknown	62 (1.3)	58 (1.6)

*Data abstracted from text fields of Georgia Cancer Registry database. AJCC = American Joint Committee on Cancer; ER = estrogen receptor; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; SES = socioeconomic status.
†Mostly military; n = 8 other among NHB; n = 0 other among NHW.

women were less likely to be married at the time of diagnosis (35% vs 61%) and more likely to live in a high-poverty neighborhood at diagnosis (45% vs 13%, 20–100% poverty index). In the metropolitan-Atlanta area, we observed an overall age-adjusted hazard ratio of 2.35 (95% CI = 2.04 to 2.72) comparing the BC specific mortality hazard in NHB women with NHW women (data not shown).

Tumor Characteristics

We observed a consistent disparity in BC deaths between NHB women and NHW women within strata of diagnostic stage (Table 2). There was a departure from additivity of the RERI for each increase in stage classification, with the most pronounced effect observed among NHB women with stage IV disease (RERI = 57, 95% CI = 27 to 88). We found similar effects for tumor grade at diagnosis. Among NHB women diagnosed with ER+ disease, we observed 2.49 times the hazard of BC mortality compared to NHW women (95% CI = 2.07 to 2.99). Within strata of molecular subtype, we observed consistent disparities indicating more than a twofold hazard of BC mortality among NHB patients diagnosed with luminal A, luminal B, or HER2-overexpressing tumors. The smallest relative disparity was among women diagnosed with TNBC (HR = 1.36, 95% CI = 1.01 to 1.82). With exception of stage, multivariable models showed similar trends but had attenuated effect estimates (Supplementary Table 1, available online).

Treatment Characteristics

Race disparities were pronounced within strata across all treatment modalities (Table 3). We observed multiplicative interaction for the type of surgery received and receipt of chemotherapy, the former likely driven by women with stage IV disease who did not undergo surgery. In age-adjusted models, we did identify additive interaction between receipt of hormone therapy (among women with ER+ disease) and race and/or ethnicity (RERI = 0.90, 95% CI = 0.77 to 1.04). Similar additive interactive effects were found for receipt of radiation therapy (RERI = 1.40, 95% CI = 0.61 to 2.19). In the multivariable-adjusted models, we observed similar, although attenuated, effect estimates (Supplementary Table 2, available online).

Patient Characteristics

BC-specific mortality disparities by race and patient characteristics are provided in Table 4. We observed the most pronounced disparity among patients with private insurance at diagnosis (HR = 2.46, 95% CI = 1.98 to 3.07) and Medicare (HR = 2.24, 95% CI = 1.74 to 2.90). We observed a larger disparity among married women (HR = 2.71, 95% CI = 2.13 to 3.45). However, there was no evidence of effect modification by marital status or departure from additivity. Among individuals living in the highest SES index, we observed that NHB women had 2.67 times the hazard compared to their NHW counterparts (95% CI = 1.65 to 4.33). Conversely, among women with no insurance and in the lowest SES index, we observed less pronounced disparities (HR = 1.56, 95% CI = 0.71 to 3.43 and HR = 1.90, 95% CI = 1.39 to 2.59, respectively). In the multivariable-adjusted models, we observed similar, but attenuated, effect estimates (Supplementary Table 3, available online).

Mediation Analysis

Based on our graphical depiction of the underlying paths relating race to BC-specific mortality, we evaluated the role of stage, subtype, and SES as mediators to the underlying disparities. In our mediation analysis, we observed that 68% (95% CI = 52% to 83%) of the excess BC-specific mortality was mediated through stage, subtype, and SES, controlling for age at diagnosis (Table 5). Given that advanced stage at diagnosis appeared to drive the association, we also performed a sensitivity analysis among stage I–III diagnoses. The total proportion mediated through these three factors remained approximately 68%, although the relative proportion mediated through SES increased (data not shown).

Discussion

Consistent with previous reports on racial disparities in BC-specific mortality, our study illustrates substantial disparities between NHB and NHW women diagnosed with BC in the metropolitan Atlanta area. Providing a more robust picture of the public health problem, our study broadly examined the contributions of tumor, treatment, and patient characteristics to the disparity, identifying potential targets for further exploration and—ultimately—intervention. Our interaction models

Table 2. Age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for breast cancer (BC)-specific death according to race and tumor characteristics among non-Hispanic White (NHW) and non-Hispanic Black (NHB) women diagnosed with BC in the metropolitan Atlanta area 2010–2014 and registered with the Georgia Cancer Registry

Characteristic	No. deaths		Common referent HR (95% CI)		RERI (95% CI)	Stratified effects HR (95% CI)	Stratified effects* HR (95% CI)
	NHW	NHB	NHW	NHB			
Stage							
I	31	29	Referent	1.97 (1.19 to 3.26)	—	2.08 (1.26 to 3.43)	1.13 (0.63 to 2.01)
II	80	118	4.75 (3.13 to 7.21)	8.96 (6.02 to 13.35)	3.25 (1.01 to 5.49)	1.89 (1.41 to 2.53)	1.42 (1.04 to 1.95)
III	85	126	18.85 (12.43 to 28.59)	29.97 (20.14 to 44.61)	10.16 (2.52 to 17.79)	1.57 (1.17 to 2.09)	1.24 (0.90 to 1.71)
IV	123	215	69.59 (46.43 to 104.3)	127.7 (87.01 to 187.4)	57.13 (26.5 to 87.75)	1.73 (1.34 to 2.22)	1.57 (1.19 to 2.06)
$P_{Interaction}$						.81	.47
Grade							
1	20	14	Referent	1.92 (0.96 to 3.87)	—	1.99 (0.98 to 4.03)	1.74 (0.70 to 4.29)
2	97	119	3.02 (1.86 to 4.91)	6.54 (4.06 to 10.53)	2.59 (0.73 to 4.46)	2.21 (1.67 to 2.92)	1.72 (1.26 to 2.35)
3+	154	286	8.24 (5.16 to 13.16)	14.43 (9.15 to 22.76)	5.26 (2.18 to 8.34)	1.71 (1.40 to 2.10)	1.14 (0.92 to 1.42)
$P_{Interaction}$						.38	.06
ER status							
ER+	209	282	Referent	2.45 (2.03 to 2.95)	—	2.49 (2.07 to 2.99)	1.62 (1.31 to 2.00)
ER-	90	189	3.37 (2.61 to 4.34)	5.32 (4.34 to 6.52)	0.51 (−0.58 to 1.59)	1.57 (1.21 to 2.02)	1.15 (0.86 to 1.53)
$P_{Interaction}$						.007	.08
Molecular subtype							
Luminal A	171	221	Referent	2.42 (1.98 to 2.95)	—	2.43 (1.99 to 2.97)	1.58 (1.25 to 1.98)
Luminal B	31	56	1.37 (0.93 to 2.01)	3.26 (2.40 to 4.43)	0.48 (−0.56 to 1.52)	2.57 (1.66 to 3.98)	1.53 (0.96 to 2.45)
HER2 overexpressing	16	40	2.29 (1.37 to 3.83)	5.59 (3.96 to 7.91)	1.88 (−0.21 to 3.98)	2.51 (1.41 to 4.46)	1.69 (0.87 to 3.30)
TNBC	65	137	3.92 (2.94 to 5.22)	5.46 (4.35 to 6.85)	0.12 (−1.24 to 1.49)	1.36 (1.01 to 1.82)	1.09 (0.78 to 1.53)
$P_{Interaction}$						.02	.16

*Adjusted for age; stage; subtype; receipt of surgery, chemotherapy, radiation, hormone therapy, and trastuzumab; insurance status. ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; RERI = relative excess risk due to interaction; TNBC = triple-negative BC.

showed the most pronounced effect estimates among lower stage, ER+, and luminal breast tumors. In nearly all analyses, disparities were exacerbated in the referent category, or group that is typically thought to have the best prognosis. Although racial disparities in BC mortality have been attributed to black women more likely being diagnosed at a later stage or with TNBC subtype, we observed the least pronounced racial disparities among patients with tumors that carry less favorable prognosis, such as TNBC subtype and high stage at diagnosis.

Tumors with a favorable prognosis are those with low stage, limited lymph node involvement, and expression of ER at diagnosis. Racial disparities in these tumors might suggest that downstream characteristics from diagnosis may be important to better understand and address the disparity. Consistent with our findings, a study that examined racial disparities within ER- and/or PR-positive tumors among NHB and NHW women in Chicago reported a fourfold increase in hazard of death for NHB women (95% CI = 1.76 to 10.9) (38,39). Tumors with positive expression of hormone receptor are amenable to biomarker-driven therapies; however, a recent study has suggested that NHB women are less likely to be adherent to adjuvant endocrine therapy, which may be related to prognosis (40). Further, data among NHB and NHW women diagnosed with luminal A disease in an equal-access health-care system (Kaiser Permanente) showed no disparities in BC-specific mortality (41). These findings may suggest that outcome disparities among NHB women with luminal A tumors are largely attributable to social and structural inequities (42) and warrant further investigation (43,44).

Our results, as well as others, have identified stage as an important contributor to the disparity. This is evident among NHB women who are consistently diagnosed at a later stage, which is one important aspect of the disparity. However, our age-adjusted models showed the most pronounced relative mortality disparity among stage I breast tumors, which was strongly attenuated after adjusting for covariates in the sensitivity analysis. These results may be driven by the low baseline risk of mortality in these women and may also suggest that treatment-related factors (timely receipt of therapy or adherence) are drivers of the observed disparity in early stage tumors. Additional efforts are needed to understand why NHB women are consistently diagnosed with later stage, despite self-report of comparable mammography rates among NHB women in national surveys (8,45), and what downstream factors from diagnosis are affecting the disparity in women diagnosed with low-stage breast carcinomas.

In a recent study by Warner et al. (46), the authors reported that molecular subtype, stage, body mass index (BMI), and insurance were important contributors to BC mortality disparities. We similarly identified stage and subtype as important contributors, in addition to SES index—accounting for nearly 68% of the disparity. BMI is not readily available in registry data, thus we were unable to examine the extent to which it mediates the association between race and BC mortality disparities. Although an important contribution to the literature, Warner et al. used the National Cancer Database, which includes women diagnosed with BC in various sites around the United States and may not be representative of the experience of women diagnosed with BC in the southeastern United States. Given that race is a social construct that encompasses a lived experience that does not have a counterfactual condition, it is important to identify modifiable factors that mediate the observed effect and could serve as targets for intervention within the social contexts' that people live (47).

Although racial disparities in BC mortality are well documented, there exists substantial geographic heterogeneity, which

Table 3. Age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for breast cancer (BC)-specific death according to race and treatment parameters among non-Hispanic white (NHW) and non-Hispanic black (NHB) women diagnosed with BC in the metropolitan Atlanta area 2010–2014 and registered with the Georgia Cancer Registry

Characteristic	No. deaths		Common referent HR (95% CI)		RERI (95% CI)	Stratified effects HR (95% CI)	Stratified effects* HR (95% CI)
	NHW	NHB	NHW	NHB			
Surgery							
No.	139	241	Referent	1.30 (1.03 to 1.64)	—	1.27 (1.01 to 1.61)	1.38 (1.07 to 1.78)
Breast conserving surgery	59	76	0.04 (0.03 to 0.06)	0.08 (0.06 to 0.11)	−0.26 (−0.55 to 0.04)	2.12 (1.49 to 3.00)	1.44 (0.96 to 2.15)
Mastectomy	121	171	0.10 (0.08 to 0.14)	0.23 (0.18 to 0.30)	−0.17 (−0.45 to 0.11)	2.25 (1.77 to 2.85)	1.39 (1.07 to 1.80)
$P_{Interaction}$						.02	.98
Chemotherapy							
No	103	124	0.34 (0.26 to 0.44)	0.97 (0.75 to 1.25)	−0.33 (−0.70 to 0.03)	3.00 (2.26 to 3.97)	1.63 (1.17 to 2.27)
Yes	171	317	Referent	1.96 (1.62 to 2.38)	—	1.92 (1.59 to 2.32)	1.38 (1.12 to 1.71)
$P_{Interaction}$						.09	.03
Radiation							
No	164	238	1.868 (1.46 to 2.38)	4.73 (3.78 to 5.91)	1.40 (0.61 to 2.19)	2.64 (2.14 to 3.27)	1.29 (0.62 to 2.64)
Yes	130	205	Referent	2.46 (1.96 to 3.09)	—	2.28 (1.81 to 2.86)	1.53 (1.19 to 1.96)
$P_{Interaction}$						.69	.68
Receipt of hormone therapy (ER+ tumors only)							
No	161	267	1.93 (1.43 to 2.60)	4.73 (3.62 to 6.19)	0.90 (0.77 to 1.04)	2.36 (1.72 to 3.25)	1.36 (0.96 to 1.93)
Yes	158	221	Referent	2.47 (1.97 to 3.09)	—	2.50 (1.99 to 3.13)	1.84 (1.42 to 2.38)
$P_{Interaction}$						.98	.37
Receipt of trastuzumab (HER2+ tumors only)							
No	283	414	1.36 (0.76 to 2.44)	3.68 (2.24 to 6.05)	0.63 (−0.88 to 2.13)	2.64 (1.53 to 4.55)	1.29 (0.63 to 2.64)
Yes	36	74	Referent	2.69 (1.70 to 4.26)	—	3.37 (1.59 to 7.14)	1.97 (1.17 to 3.32)
$P_{Interaction}$						.99	.33

*Adjusted for age; stage; subtype; receipt of surgery, chemotherapy, radiation, hormone therapy, and trastuzumab; insurance status. ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; RERI = relative excess risk due to interaction.

Table 4. Age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for breast cancer (BC)-specific death according to race and patient characteristics among non-Hispanic white (NHW) and non-Hispanic black (NHB) women diagnosed with BC in the metropolitan Atlanta area 2010–2014 and registered with the Georgia Cancer Registry

Characteristic	No. deaths		Common referent HR (95% CI)		RERI (95% CI)	Stratified effects HR (95% CI)	Stratified effects† HR (95% CI)
	NHW	NHB	NHW	NHB			
Insurance type*							
Uninsured	8	36	3.84 (1.88 to 7.84)	6.09 (4.10 to 9.04)	0.77 (−2.69 to 4.23)	1.56 (0.71 to 3.43)	1.15 (0.46 to 2.86)
Private insurance	147	212	Referent	2.47 (1.98 to 3.07)	—	2.46 (1.98 to 3.07)	1.61 (1.28 to 2.03)
Medicaid	18	93	3.18 (1.92 to 5.27)	4.56 (3.48 to 5.97)	−0.09 (−1.92 to 1.74)	1.44 (0.87 to 2.37)	1.27 (0.75 to 2.16)
Medicare	133	131	1.56 (1.17 to 2.07)	3.41 (2.61 to 4.46)	0.38 (−0.40 to 1.16)	2.24 (1.74 to 2.90)	1.45 (1.09 to 1.93)
$P_{Interaction}$						.33	.28
Age group, y							
<40	15	49	0.66 (0.38 to 1.14)	1.75 (1.25 to 2.46)	0.02 (−0.72 to 0.76)	2.68 (1.48 to 4.85)	1.68 (0.93 to 3.03)
40–49	39	102	0.55 (0.38 to 0.79)	1.56 (1.20 to 2.05)	−0.06 (−0.62 to 0.49)	2.85 (1.95 to 4.16)	1.54 (0.99 to 2.39)
50–65	124	210	0.65 (0.50 to 0.84)	1.62 (1.29 to 2.04)	−0.11 (−0.61 to 0.39)	2.50 (1.99 to 3.16)	1.43 (1.09 to 1.86)
>65	141	127	Referent	2.08 (1.61 to 2.68)	—	2.06 (1.60 to 2.66)	1.35 (1.01 to 1.80)
$P_{Interaction}$						.59	.63
Marital status							
Married	139	144	Referent	2.82 (2.21 to 3.60)	—	2.71 (2.13 to 3.45)	1.79 (1.37 to 2.34)
Single	47	170	1.64 (1.15 to 2.32)	3.87 (3.05 to 4.89)	0.41 (−0.51 to 1.33)	2.26 (1.61 to 3.17)	1.49 (1.03 to 2.17)
Divorced/widowed/ separated	116	143	1.94 (1.48 to 2.53)	3.12 (2.44 to 3.98)	−0.64 (−1.50 to 0.21)	1.51 (1.17 to 1.96)	1.07 (0.79 to 1.45)
$P_{Interaction}$						.01	.07
SES index							
0–<5% poverty	71	25	Referent	2.90 (1.78 to 4.73)	—	2.67 (1.65 to 4.33)	2.26 (1.26 to 4.06)
5–<10% poverty	96	57	1.44 (1.04 to 1.99)	3.17 (2.20 to 4.58)	−0.16 (−1.70 to 1.37)	2.07 (1.47 to 2.90)	1.17 (0.76 to 1.79)
10–<20% poverty	99	167	1.61 (1.16 to 2.23)	3.23 (2.40 to 4.35)	−0.27 (−1.67 to 1.12)	1.88 (1.44 to 2.44)	1.32 (0.97 to 1.80)
20–100% poverty	53	239	1.86 (1.27 to 2.71)	3.72 (2.80 to 4.94)	−0.04 (−1.47 to 1.40)	1.90 (1.39 to 2.59)	1.29 (0.92 to 1.81)
$P_{Interaction}$						.61	.41

*Military/other not estimated due to cell size. RERI = relative excess risk due to interaction; SES = socioeconomic status.
†Adjusted for age; stage; subtype; receipt of surgery, chemotherapy, radiation, hormone therapy, and trastuzumab; insurance status.

Table 5. Age-adjusted hazard models and 95% confidence intervals (CIs) for the mediating effects of subtype, stage, and socioeconomic status (SES) index on the association between race and breast cancer-specific death among non-Hispanic white (NHW) and non-Hispanic black (NHB) women diagnosed with breast cancer in the metropolitan Atlanta area 2010–2014 and registered with the Georgia Cancer Registry

Mediator	P(M|E)*	Indirect effect†	% mediated
Subtype	0.58	0.11 (0.09 to 0.14)	12 (8.8 to 15.8)
	0.12		
	0.05		
	0.18		
Stage	0.39	0.45 (0.36 to 0.52)	47.3 (38.2 to 57.1)
	0.37		
	0.14		
	0.094		
SES index	0.059	0.09 (0.00 to 0.20)	8.9 (0.0 to 18.1)
	0.13		
	0.36		
	0.45		
Direct effect		0.32 (0.14 to 0.51)	—
Total effect		0.96 (0.7 to 1.14)	68 (53 to 89)

*Probability of each mediator among NHB women. HR = hazard ratio.
†Effect on outcome through mediator on log scale.

reflects the distinct social conditions, local policies, cultural norms, and institutional environments throughout the United States. A meta-analysis of 20 studies reported that NHB women were 19% more likely to die from BC than their NHW counterparts (48). This meta-estimate suggests that there is an observed disparity; however, it is much less than what we observed in our study. The Carolina Breast Cancer Study has reported results that are more consistent with what we observed, with a hazard ratio of 1.9 comparing NHB to NHW women among those diagnosed with a luminal A subtype (95% CI = 1.3 to 2.8) (49). The similarity of our results with the Carolina Breast Cancer Study may suggest that distal factors related to the environment may be important contributors to differences in outcomes. These include systemic and political environments that may be more likely to occur in the southeastern United States compared to elsewhere in the United States. Health-care access, systemic racism, and receipt of guideline-concordant care could be important macro-level factors to consider in future studies.

Our study has many strengths, namely, that it leverages resources from a high-quality population-based registry among a well-defined source population. Using this information-rich data source, we were able to examine specific tumor, treatment, and patient characteristics and their contribution to BC-specific mortality. Limitations should also be considered. Trastuzumab is not recorded directly in the database and was abstracted from text fields for the purposes of this study. We expect that any patient with a recorded indication for trastuzumab would have received it, whereas, women who did not have an indication for the therapy in the text fields could have received the therapy, but these data were not recorded. In our study, approximately 70% of HER2+ women had an indication for HER2 targeted therapy, which is comparable to the proportion of ER+ women receiving endocrine therapy in SEER-Medicare linked studies (50). Still, further validation is needed. Additionally, we were unable to assess guideline receipt of the various treatment modalities or adherence to endocrine therapy, which may be important contributors to the observed differences in short-term disparities. Finally, we did not have access to information related to individual-level factors such as income, BMI, or medical and mental health complexity, which will be essential in future analyses.

Although prognostic disparities in BC are related to a complex combination of biologic, treatment, and patient-level factors, we demonstrated that there could be drivers that are amenable to intervention. Although the increased incidence rate of TNBC among NHB women has received attention, because these tumors have a poorer prognosis, our results also highlight the importance of hormonally responsive tumors as primary drivers of the disparity, which already have established and effective treatment regimens. Luminal subtypes are the most prevalent tumors among African-American women, comprising approximately 75% of all BC diagnoses (7). Effectively treating women with ER+ tumors could substantially impact race disparities in the metropolitan Atlanta area. Further understanding of differences in receipt of guideline-concordant care, treatment delay and completion, and biologic factors that may affect response to treatment and prognosis are needed to improve patient outcomes.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA *Cancer J Clin*. 2017; 67(1):7–30.
2. Guo F, Kuo Y-F, Shih YCT, et al. Trends in breast cancer mortality by stage at diagnosis among young women in the United States. *Cancer*. 2018;124(17): 3500–3509.

3. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353(17):1784–1792.
4. Group EBCTC. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687–1717.
5. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724–734.
6. Mamounas EP, Tang G, Fisher B, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. *J Clin Oncol*. 2010;28(10):1677–1683.
7. DeSantis CE, Ma J, Goding Sauer A, et al. Breast cancer statistics, 2017, racial disparity in mortality by state. *CA Cancer J Clin*. 2017;67(6):439–448.
8. American Cancer Society. *Breast Cancer Facts & Figures 2017-2018*. Atlanta, GA: American Cancer Society; 2017.
9. Hunt BR, Hurlbert MS. Black:white disparities in breast cancer mortality in the 50 largest cities in the United States, 2005–2014. *Cancer Epidemiol*. 2016;45:169–173.
10. Warnecke RB, Oh A, Breen N, et al. Approaching health disparities from a population perspective: the National Institutes of Health Centers for Population Health and Health Disparities. *Am J Public Health*. 2008;98(9):1608–1615.
11. U.S. Department of Health and Human Services. *Report of the Secretary's Task Force on Black and Minority Health*. Washington, DC: U.S. Department of Health and Human Services; 1985.
12. Institute of Medicine (US) Committee to Review the CDC Centers for Research and Demonstration of Health Promotion and Disease Prevention; Stoto MA, Green LW, Bailey LA, eds. *Linking Research and Public Health Practice: A Review of CDC's Program of Centers for Research and Demonstration of Health Promotion and Disease Prevention*. Washington, DC: National Academies Press; 1997.
13. Institute of Medicine (US) Committee on the Review and Assessment of the NIH's Strategic Research Plan and Budget to Reduce and Ultimately Eliminate Health Disparities. The National Academies Collection: Reports funded by National Institutes of Health; Thomson GE, Mitchell F, Williams MB, eds. *Examining the Health Disparities Research Plan of the National Institutes of Health: Unfinished Business*. Washington, DC: National Academies Press; 2006.
14. Koh HK, Blakey CR, Roper AY. Healthy People 2020: a report card on the health of the nation. *JAMA*. 2014;311(24):2475–2476.
15. Bauer KR, Brown M, Cress RD, et al. 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(9):1721–1728.
16. Dietze EC, Sistrunk C, Miranda-Carboni G, et al. Triple-negative breast cancer in African-American women: disparities versus biology. *Nat Rev Cancer*. 2015;15(4):248–254.
17. Newman LA, Kaljee LM. Health disparities and triple-negative breast cancer in African American women: a review. *JAMA Surg*. 2017;152(5):485–493.
18. Newman LA. Parsing the etiology of breast cancer disparities. *J Clin Oncol*. 2016;34(9):1013–1014.
19. Wu XC, Lund MJ, Kimmick GG, et al. Influence of race, insurance, socioeconomic status, and hospital type on receipt of guideline-concordant adjuvant systemic therapy for locoregional breast cancers. *J Clin Oncol*. 2012;30(2):142–150.
20. Daly B, Olopade OI. A perfect storm: how tumor biology, genomics, and health care delivery patterns collide to create a racial survival disparity in breast cancer and proposed interventions for change. *CA Cancer J Clin*. 2015;65(3):221–238.
21. US Census Bureau. Stat & County Quickfacts: Georgia 2015. https://www.census.gov/quickfacts/GA. Accessed December 5, 2018.
22. North American Association of Central Cancer Registries (NAACCR) Race and Ethnicity Work Group. *NAACCR Guideline for Enhancing Hispanic/Latino Identification: Revised NAACCR Hispanic/Latino Identification Algorithm [NHIA v2.2.1]*. Springfield, IL: NAACR; 2011.
23. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471–1474.
24. Reichman ME, Altekruse S, Li CI, et al. Feasibility study for collection of HER2 data by National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program central cancer registries. *Cancer Epidemiol Biomarkers Prev*. 2010;19(1):144–147.
25. Gradishar WJ, Anderson BO, Balassanian R, et al. Invasive breast cancer version 1.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2016;14(3):324–354.
26. Krieger N, Chen JT, Waterman PD, et al. Geocoding and monitoring of US socioeconomic inequalities in mortality and cancer incidence: does the choice of area-based measure and geographic level matter? The Public Health Disparities Geocoding Project. *Am J Epidemiol*. 2002;156(5):471–482.
27. US Census Bureau. American community survey. In *US Department of Commerce, Economics and Statistics Administration*, US Census Bureau Washington, DC; 2010. https://www.census.gov/programs-surveys/acs/guidance/comparing-acs-data/2010.html. Accessed December 1, 2018.
28. Knoble NB, Alderfer MA, Hossain MJ. Socioeconomic status (SES) and childhood acute myeloid leukemia (AML) mortality risk: analysis of SEER data. *Cancer Epidemiol*. 2016;44:101–108.
29. Kish JK, Yu M, Percy-Laurry A, et al. Racial and ethnic disparities in cancer survival by neighborhood socioeconomic status in Surveillance, Epidemiology, and End Results (SEER) Registries. *J Natl Cancer Inst Monogr*. 2014;2014(49):236–243.
30. Kleinbaum DG, Klein M. *Survival Analysis*. New York: Springer; 2010.
31. Krieger N, Davey Smith G. The tale wagged by the DAG: broadening the scope of causal inference and explanation for epidemiology. *Int J Epidemiol*. 2016;45(6):1787–1808.
32. Howards PP, Schisterman EF, Poole C, et al. "Toward a clearer definition of confounding" revisited with directed acyclic graphs. *Am J Epidemiol*. 2012;176(6):506–511.
33. VanderWeele TJ, Knol MJ. A tutorial on interaction. *Epidemiology Methods*. 2014;3(1):33–72.
34. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology*. 1992;3(5):245–546.
35. VanderWeele TJ. Mediation analysis: a practitioner's guide. *Annu Rev Public Health*. 2016;37:17–32.
36. Yu Q, Wu X, Li B, et al. Multiple mediation analysis with survival outcomes: with an application to explore racial disparity in breast cancer survival. *Stat Med*. 2019;38(3):398–412.
37. Yu Q, Li B. Mma: an R package for mediation analysis with multiple mediators. *J Open Res Softw*. 2017;5(1):11.
38. Tao L, Gomez SL, Keegan TH, et al. Breast cancer mortality in African-American and non-Hispanic white women by molecular subtype and stage at diagnosis: a population-based study. *Cancer Epidemiol Biomarkers Prev*. 2015;24(7):1039–1045.
39. Rauscher GH, Silva A, Pauls H, et al. Racial disparity in survival from estrogen and progesterone receptor-positive breast cancer: implications for reducing breast cancer mortality disparities. *Breast Cancer Res Treat*. 2017;163(2):321–330.
40. Wheeler SB, Spencer J, Pinheiro LC, et al. Endocrine therapy nonadherence and discontinuation in black and white women. *J Natl Cancer Inst*. 2019;111(5):498–508.
41. Haque R, Xu X, Shi J, et al. Breast cancer outcomes in a racially and ethnically diverse cohort of insured women. *Ethn Dis*. 2018;28(4):565–574.
42. Costantino NS, Freeman B, Shriver CD, et al. Outcome disparities in African American compared with European American women with ER+HER2- tumors treated within an equal-access health care system. *Ethn Dis*. 2016;26(3):407–416.
43. Fang P, He W, Gomez D, et al. Racial disparities in guideline-concordant cancer care and mortality in the United States. *Adv Radiat Oncol*. 2018;3(3):221–229.
44. LeMasters T, Madhavan SS, Sambamoorthi U, et al. Receipt of guideline-concordant care among older women with stage I-III breast cancer: a population-based study. *J Natl Compr Canc Netw*. 2018;16(6):703–710.
45. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin*. 2018;68(4):297–316.
46. Warner ET, Tamimi RM, Hughes ME, et al. Racial and ethnic differences in breast cancer survival: mediating effect of tumor characteristics and sociodemographic and treatment factors. *J Clin Oncol*. 2015;33(20):2254–2261.
47. VanderWeele TJ, Robinson WR. On causal interpretation of race in regressions adjusting for confounding and mediating variables. *Epidemiology*. 2014;25(4):473.
48. Newman LA, Griffith KA, Jatoi I, et al. Meta-analysis of survival in African American and white American patients with breast cancer: ethnicity compared with socioeconomic status. *J Clin Oncol*. 2006;24(9):1342–1349.
49. O'Brien KM, Cole SR, Tse CK, et al. Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. *Clin Cancer Res*. 2010;16(24):6100–6110.
50. Riley GF, Warren JL, Harlan LC, et al. Endocrine therapy use among elderly hormone receptor-positive breast cancer patients enrolled in Medicare Part D. *Medicare Medicaid Res Rev*. 2011;1(4):1.04.a04.