Racial and Socioeconomic Disparities in Cardiotoxicity Among Women With HER2-Positive Breast Cancer

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Breast cancer and cardiovascular-specific mortality are higher among blacks compared with whites, but disparities in cancer therapy-related adverse cardiovascular outcomes have not been well studied. We assessed for the contribution of race and socioeconomic status on cardiotoxicity among women with HER2-positive breast cancer. This retrospective cohort analysis studied women diagnosed with stage I-III HER2-positive breast cancer from 2004-2013. All underwent left ventricular ejection fraction assessment at baseline and at least one follow-up after beginning trastuzumab. Multivariable logistic regression was used to assess the association between race and socioeconomic status (SES) on cardiotoxicity, defined by clinical heart failure (New York Heart Association class III or IV) or asymptomatic left ventricular ejection fraction decline (absolute decrease ≥ 10% to < 53%, or ≥ 16%). Blacks had the highest prevalence of hypertension, diabetes, and increased BMI. Neighborhood-level SES measures including household income and educational attainment were lower for blacks compared with whites and others. The unadjusted cardiotoxicity risk was significantly higher in black compared with white women (OR, 2.10; 95% CI, 1.42 to 3.10). In a multivariable analysis, this disparity persisted after controlling for relevant cardiovascular risk factors (adjusted OR, 1.88; 95% CI, 1.25 to 2.84). Additional models adjusting for SES factors of income, educational attainment, and insurance status did not significantly alter the association between race and cardiotoxicity. In conclusion, black women are at increased risk of cardiotoxicity during HER2-targeted breast cancer therapy. Future etiologic analyses, particularly studies exploring biologic or genetic mechanisms, are needed to further elucidate and reduce racial disparities in cardiotoxicity. **(Am J Cardiol 2021;147:116−121)**

Advances in breast cancer research and improvements in breast cancer surveillance and treatment have led to significant survival gains for women diagnosed with breast cancer.[1] Despite these advances, racial disparities in breast cancer screening, diagnosis, and treatment have been well established in the literature, with black women more likely to be diagnosed with more advanced stages of disease and up to 40% more likely to die from breast cancer compared with white women.[2,3] Treatment for human epidermal growth factor receptor 2 (HER2) positive breast cancer with HER2-targeted therapies such as trastuzumab is associated with risk for cardiotoxicity, manifest as a decline in left ventricular ejection fraction (LVEF) or heart failure that is most commonly observed during the 12-month HER2-targeted treatment period.[4] There is limited data on whether racial or other social determinants of health (e.g. socioeconomic status, education, or access to healthcare) influence the risk of developing cardiotoxicity from breast cancer treatment.[5,6] To address this important knowledge gap, the primary objective of the current study was to evaluate for racial disparities in cardiotoxicity associated with HER2-positive breast cancer treatment. Secondary objectives were to determine whether socioeconomic factors including income, educational attainment, and insurance status account for observed racial differences in cardiotoxicity.

Methods

Women with stage I-III HER2-positve breast cancer who received trastuzumab at Memorial Sloan Kettering Cancer Center (MSKCC) between September 1, 2004 and July 1, 2013 were identified from an institutional breast cancer database of all newly diagnosed breast cancer patients. HER2-positive disease was defined by an immunohistochemical score of 3+ or by a fluorescent in−situ hybridization ratio of ≥ 2.0. Only patients who underwent a LVEF assessment at baseline and at least 1 follow-up timepoint after beginning breast cancer treatment were included in the analysis. Women of all races were included. Of 1,443 women treated at MSKCC with trastuzumab-based therapy,

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44 (39 white, 3 black, 2 other) were excluded due to insufficient LVEF assessments. This study was approved by the institutional review board of MSKCC and a waiver of informed consent was granted.

Self-reported race was categorized into three nonoverlapping groups: white, black, or other. Basic demographic information, tumor characteristics, cancer treatment, and cardiovascular history were collected by retrospective chart review. The HER2-targeted treatment period was defined by the start and end dates of trastuzumab and was ascertained from pharmacy administration records. Socioeconomic data was based upon income and education level available through the United States Census 2013-2017 American Community Survey.[7] The following neighborhood-level variables linked by zip-code were collected for each patient: median household income, percentage living below the poverty level, and percentage of adults (25 years and over) attaining less than a high school diploma. Patients were categorized into quartiles of median household income for the entire cohort in ascending order from lowest (Q1) to highest (Q4). Neighborhoods with a poverty rate ≥ 20% were classified as low-income.[8] Insurance type (Medicaid, Medicare, or private/other) was ascertained from institutional billing records.

A cardiotoxicity event included: (1) clinical heart failure, defined by symptoms such as dyspnea, decreased exercise tolerance, or fatigue during less than ordinary activity or at rest (New York Heart Association class III or IV) with evidence of new or worsening heart failure on physical examination (e.g. peripheral edema, crackles, increased jugular venous pressure, or rapid weight gain related to fluid retention) or diagnostic testing (e.g. increased B-type natriuretic peptide, pulmonary congestion on chest x-ray, or abnormal left ventricular systolic function); or (2) asymptomatic decline in LVEF, defined as an absolute decrease of ≥ 10% points from baseline to below 53% or an absolute decrease of ≥ 16% occurring during the HER2-targeted treatment period. All cardiotoxicity events were confirmed by a cardiologist based upon data abstracted from the medical record for each patient, including the following: internal and external cardiac imaging procedures (i.e. echocardiogram, multigated acquisition scan, or cardiac magnetic resonance imaging), outpatient and inpatient clinical documentation, laboratory findings, and review of pharmacy administration data to identify early interruption of HER2-targeted therapy due to cardiotoxicity.

Continuous data are summarized as mean and standard deviation or median and interquartile range as appropriate, and categorical measures as frequency and percentage. Differences in characteristics between groups were assessed using the Kruskal-Wallis test for continuous variables and Pearson's chi squared test for categorical variables. Univariable and multivariable logistic regression were used to model cardiotoxicity with race and socioeconomic variables including education, income, and insurance status. Adjusted odds ratios (ORs) with 95% confidence intervals were reported. The following covariates for which there was a plausible biological or epidemiological association with cardiotoxicity were included in the multivariable analysis: Age, body mass index (BMI), baseline LVEF, anthracycline exposure, hypertension, diabetes, coronary artery disease (CAD), and baseline beta-blocker (BB) or angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) treatment. All statistical analyses were performed using STATA 16.1 (StataCorp, College Station, Texas). A p value (2-tailed) of <0.05 was considered statistically significant.

Results

A total of 1,399 women with HER2-positive breast cancer were included in this analysis: 169 (12%) were black, 1,064 (76%) were white, 166 (12%) were other (120 Asian, 1 American Indian/Alaska Native, 1 Native Hawaiian/Pacific Islander, 44 other or refused to answer). The median age was 51 (interquartile range, 44-59) years and 1,086 (78%) received an anthracycline-based chemotherapy regimen. **Table 1** lists tumor and primary treatment characteristics by race.

At baseline, black women had a higher prevalence of cardiovascular risk factors including hypertension, diabetes, and elevated BMI (≥ 25 kg/m^2). Treatment with renin angiotensin aldosterone system antagonists (but not beta-blockers) at baseline prior to initiating HER2-targeted therapy was more common among black participants. There was no significant difference in baseline LVEF between racial groups.

Table 2 summarizes the distribution of socioeconomic characteristics by race. The median household income (by neighborhood) was lowest for black patients. The poverty rate was approximately two times higher in neighborhoods of black compared with white or other women (15.9% vs. 6.7% vs 8.2%, $p < 0.001$). Thirty-three percent of black, 9% of white, and 8% of other patients lived in a low-income neighborhood ($p < 0.001$). Neighborhood-level educational attainment was lower for black patients, with 14.3% attaining less than a high school degree compared with 6.9% for white and 8.5% for other patients ($p < 0.001$). The proportion of patients with Medicaid insurance was 12% for black, 7% for white, and 8% for other patients.

Overall, the proportion of women with the composite cardiotoxicity end point of clinical heart failure or asymptomatic LVEF decline was highest for black women (25%) compared with white (14%) or other (11%) women ($p < 0.001$). Heart failure (New York Heart Association class III/IV) occurred most often among black (7%), followed by white (2%) and other (1%) patients ($p < 0.001$). A significant LVEF decline also occurred more often among black (18%) as compared with white (12%) and other (10%) patients ($p = 0.04$). Racial differences in cardiotoxicity remained significant when the criteria for asymptomatic LVEF decline was based upon 50% as the lower limit of normal instead of 53% ($p = 0.001$). In a subset analysis of 950 women without preexisting cardiovascular risk factors (hypertension, diabetes, or hyperlipidemia) or CAD, the rate of cardiotoxicity remained highest among black (20%) compared with white (11%) or other (11%) women.

The number of LVEF assessments performed during the 12-month period after beginning HER2-targeted therapy was assessed to explore for differences in cardiotoxicity surveillance practices by racial group. Among the entire cohort, the median number of LVEF assessments was

Table 1
Clinical characteristics by race

Characteristic	Black (n = 169)	White (n = 1,064)	Other (n = 166)	p
Age (years)	51.6 (44.6, 59.3)	51.0 (43.5, 59.2)	50.9 (42.7, 57.5)	0.420
BMI (kg/m^2)	29.3 (25.8, 32.2)	25.3 (22.5, 29.3)	23.9 (21.8, 27.5)	<0.001
<25	34 (20%)	506 (48%)	96 (58%)	
25-29.9	63 (37%)	325 (31%)	50 (30%)	
≥ 30	72 (43%)	233 (22%)	20 (12%)	
Cancer Stage				0.052
I	54 (32%)	402 (38%)	54 (33%)	
II	61 (36%)	424 (40%)	74 (45%)	
III	54 (32%)	238 (22%)	38 (23%)	
ER-positive	114 (67%)	684 (64%)	88 (53%)	0.010
PR-positive	86 (51%)	519 (49%)	66 (40%)	0.080
Chemotherapy regimen				0.179
Anthracycline	128 (76%)	820 (77%)	138 (83%)	
Non-anthracycline	41 (24%)	244 (23%)	28 (17%)	
Trastuzumab dose, cumulative (mg/kg)	106 (102, 110)	106 (104, 110)	108 (104, 110)	0.001
Radiation therapy	123 (73%)	721 (68%)	113 (68%)	0.426
Baseline LVEF (%)	65 (63, 70)	65 (62, 70)	67 (64, 70)	0.438
Hypertension	68 (40%)	229 (22%)	33 (20%)	<0.001
Diabetes mellitus	28 (17%)	56 (5%)	17 (10%)	<0.001
Hyperlipidemia	31 (18%)	180 (17%)	29 (17%)	0.895
Coronary artery disease	5 (3%)	14 (1%)	4 (2%)	0.210
Smoker	37 (22%)	414 (39%)	21 (13%)	<0.001
BB at baseline	21 (12%)	84 (8%)	11 (7%)	0.099
ACEI/ARB at baseline	38 (22%)	147 (14%)	25 (15%)	0.014

Values are N (%) or median (interquartile range [IQR])

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; ER, estrogen receptor; IQR, interquartile range; LVEF, left ventricular ejection fraction; PR, progesterone receptor; SD, standard deviation.

similar among black, white, and other patients (2 vs 2 vs 3, $p > 0.05$).

Black women had a significantly higher odds of developing cardiotoxicity (unadjusted OR, 2.10; 95% CI, 1.42 to 3.10) than white women. This disparity persisted after controlling for clinical factors including age, BMI, baseline LVEF, anthracycline chemotherapy, hypertension, diabetes, CAD, and baseline treatment with BB and ACE inhibitors/ARBs (adjusted OR, 1.88; 95% CI, 1.25 to 2.84). Additional models adjusting for income (model 2), educational attainment (model 3), insurance (model 4), or all three (model 5) did not significantly alter the association between black race and cardiotoxicity (**Table 3**).

Table 2
Socioeconomic factors and individual insurance status by race

Characteristic	Black (n = 169)	White (n = 1,064)	Other (n = 166)	p
Median household income ($)*	60068 (47170, 82352)	93887 (73750, 119133)	81053 (63804, 108719)	<0.001
Median household income quartile†				<0.001
1st	99 (59%)	205 (19%)	44 (27%)	
2nd	38 (23%)	255 (24%)	54 (33%)	
3rd	20 (12%)	293 (28%)	34 (21%)	
4th	10 (6%)	305 (29%)	32 (20%)	
% of individuals below the federal poverty level‡	15.9 (9.0, 24.3)	6.7 (4.4, 11.4)	8.2 (5.1, 13.2)	<0.001
Low income§	55 (33%)	92 (9%)	13 (8%)	<0.001
Individuals with less than a high-school education‖ (%)	14.3 (9.7, 21.7)	6.9 (4.5, 11.6)	8.5 (5.2, 13.9)	<0.001
Insurance type				0.135
Medicaid	21 (12%)	75 (7%)	13 (8%)	
Medicare	49 (29%)	293 (28%)	42 (25%)	
Private/other	99 (59%)	696 (65%)	111 (67%)	

Values are N (%) or median (interquartile range).

* Median household income based on patient's zip code.

† Median household income based on patient's zip code, per quartile. 1st quartile: < $65,229; 2nd quartile: $65,230 to $87,995; 3rd quartile: $87,996 to $114,423; 4th quartile: > $114,423.

‡ Percentage of persons in patient's zip code with income below the federal poverty level.

§ Persons residing in a zip code with a poverty rate ≥ 20%.

‖ Percentage of persons in patient's zip code with less than a high-school degree.

Table 3
Multivariable analysis of cardiotoxicity by race and socioeconomic factors*

Characteristic	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)
Race					
Black	1.88 (1.25, 2.84)	1.85 (1.20, 2.83)	1.94 (1.25, 3.00)	1.91 (1.26, 2.89)	1.92 (1.23, 2.98)
Other	0.76 (0.45, 1.30)	0.76 (0.45, 1.30)	0.73 (0.43, 1.27)	0.77 (0.45, 1.30)	0.74 (0.43, 1.28)
White	Reference	Reference	Reference	Reference	Reference
Low Income†					
Yes		1.08 (0.69, 1.71)			1.19 (0.68, 2.10)
No		Reference			Reference
Education level‡			1.01 (0.81, 1.24)		1.04 (0.80, 1.34)
Insurance type					
Medicare				0.90 (0.59, 1.39)	0.93 (0.61, 1.44)
Medicaid				0.69 (0.37, 1.28)	0.70 (0.38, 1.31)
Private/other				Reference	Reference

* Adjusted for age, body mass index, baseline left ventricular ejection fraction, treatment with an anthracycline-based regimen, hypertension, diabetes mellitus, coronary artery disease, baseline treatment with beta-blockers, and baseline treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

† Residing in a zip code with a poverty rate ≥ 20%.

‡ Per 10% increase in % of individuals with less than a high school education.

Discussion

This large urban single center cohort study demonstrates a significant racial disparity in cardiotoxicity among women with early HER2-positive breast cancer treated with HER2-targeted therapies. The incidence of clinical heart failure was 7% among black women, more than three times higher than white (2%) or other (1%) women. The incidence of the composite cardiotoxicity end point of clinical heart failure or significant LVEF decline was nearly two times higher in black women (25%) compared with white women (14%). Cardiovascular risk factors including hypertension, diabetes, and obesity, and low socioeconomic status were more common in black women. After adjusting for these differences in a multivariable analysis, race remained independently associated with cardiotoxicity.

Black patients have poorer cardiovascular health and higher cardiovascular disease-related mortality than whites, which has largely been attributed to a higher prevalence of cardiovascular risk factors such as hypertension, diabetes, and obesity.[9] In the Multi-Ethnic Study of Atherosclerosis study, black patients had a 1.8 times higher risk of developing heart failure compared with white patients, however this difference was attributed to the higher prevalence of hypertension and diabetes after adjustment in multivariable models.[10] The current study similarly showed a higher prevalence of hypertension and diabetes among black compared with white women with breast cancer, both of which are known risk factors for cardiotoxicity associated with anthracycline chemotherapy and/or HER2-targeted therapy.[11] Downregulation of HER2 signaling has been shown to contribute to the development of heart failure in animal models of left ventricular pressure overload, which provide mechanistic insight into the possible cardioprotective role that HER2 signaling plays in patients with hypertensive heart disease.[12,13] In the current study, 80% of black women were overweight or obese, compared with only 53% and 42% of white and other women, respectively. In a meta-analysis by Guenancia et al. of nearly 9,000 patients in 15 studies, the odds of developing cardiotoxicity was 38% higher in overweight and obese patients compared with normal-weight patients.[14] Race remained significantly associated with cardiotoxicity after adjusting for these cardiovascular risk factors, suggesting that the higher prevalence of hypertension, diabetes, and overweight/obesity alone do not fully account for the disparity of cardiotoxicity among black women.

Low socioeconomic status impacts on both quality and access to healthcare and is associated with adverse cancer and cardiovascular outcomes,[15,16] but no prior studies have evaluated the influence of socioeconomic status on cardiotoxicity. Neighborhood-level estimates for socioeconomic status including income level, educational attainment, and insurance status were consistently lower among black women in this study compared with white or other. However, these socioeconomic factors were not associated with cardiotoxicity and did not affect the magnitude of association between race and cardiotoxicity. Although all patients in this study were treated at a single institution with uniform access and quality of healthcare services, the possibility of racial heterogeneity in other unmeasured social determinants of health such as financial barriers of medical or drug expenses, housing or transportation, access to recreational facilities for exercise, or employee benefits (e.g. paid sick leave, access to childcare or eldercare) were not evaluated in the current study and cannot be excluded.

Routine surveillance for cardiac dysfunction with echocardiography is recommended by current guidelines to prevent adverse cardiac outcomes in breast cancer patients.[17] However, two population-based studies of breast cancer patients treated with trastuzumab have shown that adherence to these surveillance recommendations is below 50%.[18,19] Furthermore, findings from a recent case-control study by our group suggests that identification of an abnormal LVEF during a surveillance echocardiogram is a powerful indicator that a patient is at high risk for developing heart failure during HER2-targeted therapy.[20] Thus, efforts to improve guideline adherent cardiac surveillance may improve cardiac outcomes and could be justified as one possible solution to mitigate the risk of cardiotoxicity for

women who underwent breast cancer treatment, particularly among high-risk groups.

Consideration of biological or genetic mechanisms is necessary to further investigate the racial differences in cardiotoxicity. Pharmacoethnicity, defined as racial or ethnic diversity in drug response or toxicity, is a recognized factor accounting for variability in efficacy or tolerance to cancer therapeutics.[21] The emergence of pharmacogenetics has enhanced our understanding of racial differences in response to several cardiovascular drugs such as warfarin, beta-blockers, and ACE-inhibitors or ARBs.[22] Wide variation in individual susceptibility to the cardiotoxic effects of anthracyclines and HER2-targeted therapy for breast cancer treatment further suggest a possible genetic role, and single nucleotide polymorphisms within HER2[23,24] as well as genes relevant to anthracycline metabolism [25] have been associated with risk of cardiotoxicity. Further studies to explore racial differences in the frequency of SNPs associated with cardiotoxicity are warranted.

The present study is limited by the modest proportion of black women included despite the overall large sample size. Although large population-based studies of cardiotoxicity have previously been performed,[26,27] they rely on methodology using claims-based algorithms to ascertain cardiotoxicity events which has only moderate positive predictive value and leads to significant misclassification of cardiotoxicity events.[28] To our knowledge this is the largest study to-date investigating racial disparities on cardiotoxicity events that have been rigorously adjudicated by a cardiologist through detailed review of chart abstracted data. A further limitation of the present study was that all participants were insured and received care at a resource-rich academic center, limiting the heterogeneity of socioeconomic factors that exists in the general population and thus limiting generalizability. Findings from this study should be confirmed in an independent dataset inclusive of patients with greater socioeconomic diversity. Data on the severity of cardiovascular risk factors (i.e. hypertension, diabetes), specific type or dosage of concomitant cardiovascular medications, or the adequacy of treatment of these conditions was unavailable and could not be included in multivariable models. Finally, adjustments for socioeconomic factors including income and educational attainment were based upon United States census data linked at the neighborhood and not individual level, however this strategy has previously been used to investigate socioeconomic effects on health outcomes[29,30] and has been useful for assessing health disparities in an urban tertiary referral healthcare network.[7]

In conclusion, black women disproportionately carry the highest risk of cardiotoxicity during HER2-targeted therapy for breast cancer, and the association between race and cardiotoxicity remains robust after adjusting for the higher prevalence of cardiovascular risk factors and low socioeconomic status. Cardiovascular risk factor modification and routine cardiac imaging remain important strategies to prevent cardiotoxicity and should be encouraged for all at-risk patients receiving cardiotoxic cancer therapy. Further studies to explore biologic or genetic mechanisms of cardiotoxicity are needed to elucidate racial differences in cardiotoxicity, which will help to more accurately estimate an individual patient's risk for cardiotoxicity and personalize their care.

Credit Author Statement

Mohammed Al-Sadawi: Data curation, investigation, and writing-review and editing. **Yasin Hussain**: Data curation, investigation, and writing-review and editing. **Robert S. Copeland-Halperin**: Data curation, investigation, and writing-review and editing. **Jonathan N. Tobin**: Investigation, writing-review and editing. **Chaya S. Moskowitz**: Investigation, formal analysis, and writing-review and editing. **Chau T. Dang**: Investigation, and writing-review and editing. **Jennifer E. Liu**: Investigation, and writing-review and editing. **Richard M. Steingart**: Conceptualization, investigation, and writing-review and editing. **Michelle N. Johnson**: Conceptualization, investigation, methodology, writing-original draft, and writing-review and editing. **Anthony F. Yu**: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, writing-original draft, and writing-review and editing.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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