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A balancing act: racial disparities in cardiovascular disease mortality among women diagnosed with breast cancer

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Abstract

Background—The cardiotoxic effects of breast cancer therapies are well documented in clinical trials. However, clinical trials often underrepresent those at highest risk for cardiovascular disease (CVD)related outcomes and have limited generalizability to the larger breast cancer population. In addition, racial differences in treatment-associated CVD mortality have yet to be explored. In this study, we sought to quantify the relationship between breast cancer therapies and CVD mortality, and explore whether this effect differed between non-Hispanic black (NHB) and white (NHW) women.

Methods—Using data from the Georgia Cancer Registry, we identified women diagnosed with a first primary invasive breast cancer [2010–2014], residing in the metropolitan Atlanta area (n=3,580 NHB; n=4,923 NHW), and followed them for mortality through December 31, 2018. Exposures of interest included therapies with potential cardiotoxic effects including chemotherapy and hormone therapy, which are routinely collected by the GCR. Individual agents are not captured within the GCR, therefore trastuzumab was identified using natural language processing of textual descriptions. We used propensity score weighted Cox proportional hazards regression to

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki and has been approved by the institutional review board (IRB) of Emory University (IRB00099875) on 24 October 2017. Participant consent was not required due to the registry-based nature of the study.

calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between each treatment modality and CVD mortality among the overall cohort and by race.

Results—In the overall cohort, similar hazards of CVD mortality were found among women treated with chemotherapy (HR =1.10, 95% CI: 0.62, 1.96) and hormone therapy (HR =0.94, 95% CI: 0.59, 1.50), compared to women who did not receive the respective treatments. In contrast, women treated with trastuzumab had a higher hazard of CVD mortality compared to women not treated with trastuzumab (HR =2.05, 95% CI: 0.76, 5.52). In race-specific models, hormone therapy was associated with a higher hazard of CVD mortality among NHB women (HR =2.18, 95% CI: 0.78, 6.12), but not NHW women (HR =0.66, 95% CI: 0.39, 1.13). Similar, albeit attenuated, associations were found for chemotherapy. We were unable to investigate race-specific effects of trastuzumab due to low prevalence and insufficient number of events.

Conclusions—In our study, we observed more pronounced associations of chemotherapy and hormone therapy with CVD mortality among NHB women, for whom we know have greater CVD-related comorbidities at breast cancer diagnosis. Patients may benefit from treatment plans that find a balance between curative breast cancer treatment and prevention of CVD-related events and mortality. CVD-related outcomes may be most relevant for women with hormone receptor positive disease due to shared risk factors (e.g., obesity, tobacco use, physical activity) and longer survival.

Keywords

Breast neoplasms; cardiotoxicity; health disparities; cardiovascular diseases; mortality

Introduction

Breast cancer remains the most commonly diagnosed malignancy among women and is at the vanguard of precision medicine, with targeted therapies aimed at curing patients of their disease (1). While these therapies are effective at improving breast cancer outcomes, with an average 5-year survival of 90% (2), the cardiotoxic effects of therapies are well-documented (3). Recent evidence suggests that breast cancer survivors are at greater risk for cardiovascular disease (CVD) mortality (4), relative to women without breast cancer, manifesting approximately 7 years after diagnosis (5).

Evidence documenting the long-term effects of these therapies largely comes from clinical trials (6–8). However, breast cancer patients that participate in clinical trials are often healthier than the larger breast cancer population, and without underlying comorbidities (9,10). In addition, minority populations, such as non-Hispanic black (NHB) women, are underrepresented in clinical trial populations (11), and are more likely to present with obesity and other comorbidities at diagnosis compared to their non-Hispanic white (NHW) counterparts (12,13), potentially increasing susceptibility to CVD-related events (14,15).

Information gleaned from population-based observational studies can inform interventions over the course of treatment and follow-up care recommendations for breast cancer patients to mitigate adverse effects of treatment. However, few studies have examined the long-term effects of these therapeutic agents in population-based settings, and those doing so have

yielded inconsistent findings (16,17). This may be due to methodologic challenges—such as competing risks and confounding by indication—in observational studies that make the calculation of reliable estimates difficult (3,14). Confounding by indication can occur in studies when treatment is not randomized; women with poorer prognosis are more likely to receive treatments and die of breast cancer, potentially leading to erroneous conclusions that curative treatments are harmful with respect to breast cancer mortality (18). As breast cancer mortality competes with CVD mortality, confounding by indication could potentially explain findings that suggest cardiotoxic treatments are protective against CVD mortality (19). In this study, we used methods to mitigate potential bias due to confounding by indication and competing events to quantify the effect of breast cancer therapies on CVD mortality, and evaluate racial differences in the effect of these therapies on CVD mortality.

Methods

The Georgia Cancer Registry (GCR) is a statewide population-based registry that has collected nearly all cancer cases diagnosed among Georgia residents since January 1, 1995. Using this registry, we identified 3,580 NHB and 4,923 NHW women with a first primary invasive breast cancer diagnosis [2010–2014]. Women were included if they resided in the metropolitan-Atlanta area at the time of diagnosis and excluded if they were <18 years of age or had an autopsy diagnosis. Underlying cause of death was determined directly from death certificates and CVD mortality was defined using the International Classification of Diseases (ICD), tenth revision codes I00-I99 (ICD-9 codes 390–459). The GCR links annually to the State Office of Vital Records to identify in-state deaths, and the US National Death Index to identify deaths that occur outside of Georgia. Follow-up information was available for women through December 31, 2018. This study was conducted in accordance with the Declaration of Helsinki and has been approved by the institutional review board (IRB) of Emory University (IRB00099875) on 24 October 2017. Participant consent was not required due to the registry-based nature of the study.

Patient treatment information is routinely collected by the GCR. For the purposes of this analysis, treatments considered included radiation therapy, chemotherapy, hormone therapy and HER2-targeted therapies (trastuzumab). Individual agents are not captured within the GCR in discrete fields, therefore textual descriptions, required in Georgia for all cancer treatments, were algorithmically searched to identify records that suggested trastuzumab receipt.

We used propensity score weighting to mitigate confounding by indication in analyses of the effect of breast cancer treatments on breast cancer mortality, which allows for more reliable estimation of CVD mortality. This method creates comparable populations balanced on potential confounders, specifically those related to indication for the specified therapies or underlying disease severity (20). Estimates of association for each treatment modality with CVD mortality were calculated using average treatment effect among the treated (ATT)-weights (21). These weights make the covariate distribution among those who did not receive each therapy comparable to those who did receive the therapy. Propensity score models included the following variables for all treatment modalities: age, stage, surgery, radiation therapy, insurance status, poverty level, and race, as well as interaction terms

between race and all remaining variables in the model. Models additionally included tumor subtype and chemotherapy in hormone therapy and trastuzumab models, and estrogen receptor (ER) status and lymph node involvement in chemotherapy models. We used standardized differences (22) to assess the covariate balance across treatment within race strata, which were adequate (<0.20) for all treatments except radiation therapy (Tables S1–S4), suggesting that reliable estimates for the association of radiation therapy with CVD mortality could not be computed in our dataset and was excluded from this analysis. ATT-weights were used in Cox proportional hazards models, which censor competing causes of death at the time of death, to estimate the cause-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between each breast cancer treatment modality and CVD mortality, as well as within race group. We also conducted propensity score weighted (based on ATT-weights) analyses using Fine-Gray models, an alternate method that accounts for the presence of competing causes of death by including those who died from competing causes in the risk set (23), to produce subdistribution hazard ratios (sdHR).

Information on comorbidities at diagnosis are not collected in the GCR registry. To account for the potential for unmeasured confounding by comorbidities, namely CVD at diagnosis, we performed a quantitative bias analysis (24,25). To perform the bias analysis, we assigned values to the bias parameters based on existing literature and clinical input for the association between CVD and CVD mortality, the association between CVD and the exposures, and the prevalence of CVD among the source population (i.e., breast cancer survivors). Women with CVD and multiple comorbidities at diagnosis are less likely to receive breast cancer therapies (26), although there is limited literature on the topic, we assigned an HR =0.70 for the bias analysis. A CVD diagnosis and presence of CVD related lifestyle factors are strongly associated with CVD mortality, we assigned an HR =4.2 based on a recent publication (27). Finally, the estimated prevalence of CVD among breast cancer patients is 29.2% (28). Using the above values of bias parameters, we performed a multidimensional bias analysis to account for unmeasured confounding.

In a sensitivity analysis, we repeated the analyses among stage I–III breast tumors, as women diagnosed with stage IV disease are less likely to die from side effects of the treatment, but more likely to die from their disease.

Results

Overall, we observed 172 CVD-related deaths (10% of all deaths) with a similar proportion of CVD-related deaths, out of the total study population at risk, among NHB (2.0%) and NHW women (2.1%) (Table 1). Frequencies of CVD-related deaths according to breast cancer therapy and race/ethnicity can be found in Table S5. NHB women were more likely to receive chemotherapy (57% *vs.* 40%) and trastuzumab (14% *vs.* 11%), but less likely to receive hormone therapy (55% *vs.* 64%) compared to their NHW counterparts. The median follow-up time was 4.7 years (interquartile range =3.4–6.3 years).

In the weighted cohort, the hazard of CVD mortality was similar among women who received chemotherapy (HR =1.10, 95% CI: 0.62, 1.96) and hormone therapy (HR =0.94, 95% CI: 0.59, 1.50), relative to women who did not receive the respective therapies (Table

2). Conversely, the hazard of CVD mortality was somewhat higher among women who received trastuzumab (HR =2.05, 95% CI: 0.76, 5.52).

In models examining racial differences, among women who received chemotherapy, relative to those who did not, we observed a higher hazard of CVD mortality in NHB women (HR =1.45, 95% CI: 0.60, 3.51) but not NHW (HR =0.86, 95% CI: 0.40, 1.88). Similar trends were observed among women who received hormone therapy (NHB: HR =2.18, 95% CI: 0.78, 6.12; NHW: HR =0.66, 95% CI: 0.39, 1.13). Due to a limited number of CVD events among women who received trastuzumab (n=9), we were unable to estimate race-specific associations. Supplemental analyses accounting for the influence of non-CVD deaths on CVD-mortality yielded similar results to primary analyses, except that associations with chemotherapy and hormone therapy with CVD mortality were slightly stronger among NHB women (Table S6).

In our quantitative bias analysis accounting for the possible unmeasured confounding due to comorbid conditions such as CVD at diagnosis, results suggest that there was a slight bias in the negative direction and that adjusting for the presence of CVD at diagnosis would strengthen the observed estimates of association (Table 3). Additionally, results were similar after excluding women diagnosed with stage IV breast cancer, though less precise (Table S7).

Discussion

In this population-based study, we observed a higher hazard of CVD mortality among women who received trastuzumab. We also observed higher hazards of CVD mortality among NHB women who received chemotherapy or hormone therapy, but not among NHW women. Our findings may have important clinical implications, as the results suggest that clinicians should consider the best strategy to provide curative treatment for breast cancer patients, while simultaneously minimizing potential treatment-related cardiotoxicities, particularly among NHB women.

To our knowledge, our study is the first population-based study to report higher hazards of CVD mortality among women who received trastuzumab, compared to women who did not. Our findings could be due to chance, as the prevalence of trastuzumab receipt was low and few CVD deaths occurred over the course of study follow-up. Previously, an observational study conducted among European women diagnosed with HER2-positive early breast cancer and treated with trastuzumab found most cardiac events were asymptomatic or mild and few women died due to cardiac-related events (0.2%) (29). In contrast, we observed a higher incidence of CVD mortality (~2%), likely due to differences in study populations, as the prevalence of heart disease in the US is almost twice the prevalence in Europe (30). Evidence from clinical trials suggest trastuzumab is associated with left ventricular dysfunction and heart failure, although the overall incidence of events appears low (0% to 7.2%) and mostly reversible (6,31–33). However, participants in clinical trials often differ from women in a real-world setting with respect to age, race, and comorbid conditions (9,10), all of which are risk factors for CVD-related events that could increase susceptibility to the cardiotoxic effects of treatment. Previous population-based studies conducted in the

US have suggested higher rates of trastuzumab-related cardiotoxicity than those reported in clinical trials, particularly among older breast cancer survivors and those with underlying conditions (34,35). The well-recognized toxic effects of trastuzumab have led clinicians and researchers to reconsider the optimal duration of treatment, and recent evidence suggests that among women with HER2-positive early breast cancer, shortening the treatment duration from 12 to 6 months resulted in similar efficacy, while reducing cardiotoxicities and other adverse events (36).

In this study, we observed higher hazards of CVD mortality among NHB women who received chemotherapy or hormone therapy, but not among NHW women. In our previous analysis, we reported higher hazards of CVD mortality among NHB women relative to their NHW counterparts (15). The present findings suggest that treatment may contribute to the previously observed disparities in CVD mortality among breast cancer survivors. NHB women are more likely to be diagnosed with aggressive tumors (37) and with a higher stage disease (38). As a result, NHB women are more likely to receive anthracycline-based chemotherapy regimens, which may explain the disparate results, as anthracyclines have known cardiotoxic effects (3,39). Evidence from clinical trials suggest that hormone therapy use, particularly long-term use of aromatase inhibitors (AIs), may increase risk of CVD-related events, though the overall incidence of events remains low (3,40). However, in one of the trials, the risk of CVD-related events among women treated with AIs was higher among women with pre-existing heart disease (17% in the anastrozole arm compared to 10% in the tamoxifen arm) (41), resulting in a recommendation from the US Food and Drug Administration to weigh both the risks and benefits of anastrozole use in this subset of patients (42). The observed association among NHB women who received hormone therapy in our study may be due, in part, to the presence of underlying comorbidities (e.g., obesity and hypertension) that are more common among NHB women, especially those with hormone receptor positive disease. Other common risk factors for both CVD and breast cancer include age, hormone replacements, diet, tobacco use, alcohol intake, and physical activity (3). However, in our quantitative bias analysis assessment, the bias due to unmeasured confounding by underlying comorbidities likely biased the results in the negative direction and would not account for our findings.

This prospective study is the first population-based study to examine differences in various treatment-associated CVD mortality among NHB and NHW women. This is particularly important as women with preexisting comorbidities, including CVD-related risk factors that increase the risk of treatment-associated cardiotoxicity and are more common among NHB women, are often excluded from clinical trials. This study is limited by the breast cancer therapies ascertained from the GCR, which reports under ascertainment of treatments that may have led to misclassification of the exposure, and by lack of information on many known cardiovascular risk factors. In addition, we were unable to determine the specific chemotherapeutic agents or the cumulative dosage, important factors in determining chemotherapy-related cardiotoxicity. Lastly, estimates of association reported in this study for all treatments are imprecise due to the methodological limitations of the approach and the limited number of outcomes in the relatively short follow-up.

Our results suggest that receipt of trastuzumab may increase the risk of CVD mortality among women with breast cancer and that chemotherapy and hormone therapy may increase the risk of CVD mortality among NHB women. Among US breast cancer survivors, rates of mortality due to CVD-related events are higher than that of breast cancer, particularly among NHB women (3), highlighting the importance of managing both CVD and cancer. Breast cancer patients, especially NHB women, would benefit from clinician assessment of cardiac risk profiles to identify and manage CVD risk factors and guide treatment decisions that balance the need for both curative cancer treatment and prevention of CVD-related events and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Participant characteristics among non-Hispanic white (NHW) and black (NHB) women diagnosed with stage I-IV breast cancer between 2010 and 2014 in the Metropolitan Atlanta area (n=8,523)

Variable	Total (N=8,523)	NHW (N=4,943)	NHB (N=3,580)
Age at diagnosis, mean (SD)	58.4 (13.3)	59.9 (13.3)	56.4 (13.0)
Insurance, n (%)			
Uninsured	201 (2.4)	57 (1.2)	144 (4.0)
Private/military	5,150 (60.4)	3,140 (63.5)	2,010 (56.1)
Medicaid	655 (7.7)	139 (2.8)	516 (14.4)
Medicare	2,389 (28.0)	1,545 (31.3)	844 (23.6)
Missing	128 (1.5)	62 (1.3)	66 (1.8)
Poverty[†], n (%)			
0–<5%	1,740 (20.4)	1,529 (30.9)	211 (5.9)
5–<10%	1,924 (22.6)	1,469 (29.7)	455 (12.7)
10–<20%	2,617 (30.7)	1,320 (26.7)	1,297 (36.2)
20–100%	2,242 (26.3)	625 (12.6)	1,617 (45.2)
Stage, n (%)			
I	4,124 (48.4)	2,727 (55.2)	1,397 (39.0)
II	2,878 (33.8)	1,537 (31.1)	1,341 (37.5)
III	949 (11.1)	444 (9.0)	505 (14.1)
IV	572 (6.7)	235 (4.8)	337 (9.4)
Subtype, n (%)			
Luminal A	5,585 (65.5)	3,511 (71.0)	2074 (57.9)
Luminal B	957 (11.2)	525 (10.6)	432 (12.1)
HER2-enriched	357 (4.2)	172 (3.5)	185 (5.2)
Triple negative	1,047 (12.3)	401 (8.1)	646 (18.0)
Missing	577 (6.8)	334 (6.8)	243 (6.8)
Laterality, n (%)			
Right side	4,251 (49.9)	2,505 (50.7)	1,746 (48.8)
Left side	4,253 (49.9)	2,431 (49.2)	1,822 (50.9)
Missing	19 (0.2)	7 (0.1)	12 (0.3)

Variable	Total (N=8,523)	NHW (N=4,943)	NHB (N=3,580)
Surgery type, n (%)			
None	872 (10.2)	344 (7.0)	528 (17.7)
bcs	4,092 (48.0)	2,492 (50.4)	1,600 (44.7)
Mastectomy/radical	3,555 (41.7)	2,105 (42.6)	1,450 (40.5)
Radiation, n (%)			
No/discordant*	3,342 (39.2)	1,974 (39.9)	1,368 (38.2)
Yes	4,807 (56.4)	2,805 (57.7)	2,002 (55.9)
Missing	374 (4.4)	164 (3.3)	210 (5.9)
Chemotherapy, n (%)			
No/discordant*	4,323 (50.7)	2,866 (58.0)	1,457 (40.7)
Yes	3,997 (46.9)	1,962 (39.7)	2,035 (56.8)
Missing	203 (2.4)	115 (2.3)	88 (2.5)
Hormone therapy, n (%)			
No	3,061 (35.9)	1,590 (32.2)	1,471 (41.1)
Yes	5,151 (60.4)	3,182 (64.4)	1,969 (55.0)
Missing	311 (3.6)	171 (3.5)	140 (3.9)
Trastuzumab, n (%)			
No	7,461 (87.5)	4,395 (88.9)	3,066 (85.6)
Yes	1,062 (12.5)	548 (11.1)	514 (14.4)
Lymph node involvement, n (%)			
Negative	5,080 (59.6)	3,181 (64.4)	1,899 (53.0)
Positive	2,482 (29.1)	1,307 (26.4)	1,175 (32.8)
Not examined	961 (11.3)	455 (9.2)	506 (14.1)
Cause of death, n (%)			
Alive	6,824 (80.1)	4,139 (84.0)	2,685 (75.0)
CVD mortality	172 (2.0)	102 (2.1)	70 (2.0)
BC mortality	1,056 (12.4)	434 (8.8)	622 (17.4)
Other mortality	471 (5.5)	268 (5.4)	203 (5.7)

†, percentage of census tract at or below the federal poverty line

*, discordant therapy refers to recommendation for therapy, but not given due to patient preference or contraindication.

Table 2

Hazard ratios (HR) and 95% confidence intervals (95% CI) for cardiovascular disease-specific death overall and according to race among women diagnosed with stage I–IV breast cancer in the metropolitan Atlanta Area

Treatment	HR (95% CI)			Interaction P value
	Overall	Non-Hispanic White	Non-Hispanic Black	
Chemotherapy*				0.26
Yes	1.10 (0.62, 1.96)	0.86 (0.40, 1.88)	1.45 (0.60, 3.51)	
No/discordant	Reference	Reference	Reference	
Hormone therapy†				0.05
Yes	0.94 (0.59, 1.50)	0.66 (0.39, 1.13)	2.18 (0.78, 6.12)	
No/discordant	Reference	Reference	Reference	
Trastuzumab†				-
Yes	2.05 (0.76, 5.52)	Not estimable		
No/unknown	Reference			

Estimates for radiation therapy were unreliable and therefore excluded from this analysis.

*, propensity score model Included: age, stage, surgery, radiation therapy, insurance status, poverty level, estrogen receptor, node status, and race, as well as interaction terms between race and all variables in the model

†, propensity score models included: age, stage, surgery, radiation therapy, insurance status, poverty level, subtype, chemotherapy and race, as well as interaction terms between race and all variables in the model.

Table 3

Quantitative bias analysis accounting for possible unmeasured confounding due to presence of comorbid conditions at diagnosis

Breast cancer therapy	Observed association, HR (95% CI)	Bias parameters			HRc	Bias-adjusted estimate
		HR_{CD}	HR_{CE}	p		
Chemotherapy	1.10 (0.62, 1.96)	4.2	0.8	0.29	0.93	1.19
		4.2	0.8	0.4	0.93	1.19
		4.2	0.7	0.29	0.89	1.24
		4.2	0.7	0.4	0.89	1.24
		7.5	0.8	0.29	0.90	1.22
		7.5	0.7	0.4	0.85	1.29
Hormone therapy	0.94 (0.59, 1.50)	4.2	0.8	0.29	0.93	1.01
		4.2	0.8	0.4	0.93	1.01
		4.2	0.7	0.29	0.89	1.06
		4.2	0.7	0.4	0.89	1.06
		7.5	0.8	0.29	0.90	1.04
		7.5	0.7	0.4	0.85	1.10
Trastuzumab	2.05 (0.76, 5.52)	4.2	0.8	0.29	0.93	2.21
		4.2	0.8	0.4	0.93	2.21
		4.2	0.7	0.29	0.89	2.31
		4.2	0.7	0.4	0.89	2.32
		7.5	0.8	0.29	0.90	2.27
		7.5	0.7	0.4	0.85	2.41

HR_{CD} is the estimated hazard ratio for the association between comorbid conditions at breast cancer diagnosis and cardiovascular disease mortality. HR_{CE} is the estimated hazard ratio for the association between comorbid conditions at breast cancer diagnosis and receipt of breast cancer therapies. P is the estimated prevalence of comorbid conditions present at breast cancer diagnosis among breast cancer survivors. HR_C is the estimated hazard ratio due to confounding by comorbid conditions.