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Influence of clinical, societal, and treatment variables on racial differences in ER–/PR– breast cancer survival

M. E. Roseland¹, K. Schwartz^{2,3}, J. J. Ruterbusch³, L. Lamerato⁴, R. Krajenta⁴, J. Booza², Michael S. Simon^{3,5}

¹Wayne State University School of Medicine, Detroit, MI, USA

²Department of Family Medicine & Public Health Sciences, Wayne State University, Detroit, MI, USA

³Population Studies and Prevention Program, Karmanos Cancer Institute at Wayne State University, 4100 John R HW4HO, Detroit, MI 48201, USA

⁴Department of Public Health Sciences, Henry Ford Health Systems, Detroit, MI, USA

⁵Department of Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA

Abstract

Background—African American (AA) women with breast cancer have persistently higher mortality compared to whites. We evaluated racial disparities in mortality among women with estrogen receptor (ER)/progesterone receptor (PR)-negative breast cancer.

Methods—The study population included 542 women (45% AA) diagnosed with ER/PR-negative Stage I through III breast cancer treated at the Henry Ford Health System (HFHS) between 1996 and 2005. Linked datasets from HFHS, Metropolitan Detroit Cancer Surveillance System, and the U.S. Census Bureau were used to obtain demographic, socioeconomic, and clinical information. Economic deprivation was categorized using a previously validated deprivation index, which included 5 categories based on the quintile of census tract socioeconomic deprivation. Cox proportional hazards models were used to assess the relationship between race and mortality.

Results—AA women were more likely to have larger tumors, have higher Charlson Comorbidity Indices (CCI), and to reside in economically deprived areas. In an unadjusted analysis, AA women demonstrated a significantly higher risk of death compared to whites [hazard ratio (HR) 1.47, 95% confidence interval (CI) 1.09–2.00]. Following adjustment for clinical factors (age, stage, CCI) and treatment (radiation and chemotherapy), AA race continued to have a significant impact on mortality (HR 1.51, CI 1.10–2.08 and HR 1.63, CI 1.20–2.21). Only after adjusting for deprivation was race no longer significant (HR 1.26, CI 0.84–1.87).

Conclusions—Social determinants of health play a large role in explaining racial disparities in breast cancer outcomes, especially among women with aggressive subtypes.

Michael S. Simon, simonm@karmanos.org.

Conflicts of interest There are no conflicts of interest claimed by any of the authors.

Keywords

Hormone receptor negative breast cancer; African Americans; Survival; Socioeconomic status; Racial disparities

Introduction

While overall breast cancer mortality has gradually decreased in the United States, differences in survival are still observed between African American (AA) and white women [1, 2]. AA survival disparities likely have many underlying causes, including screening and treatment patterns, socioeconomic status (SES), and differences in tumor biology [1, 3–5].

Existing literature has shown that AA women are diagnosed more often and at younger ages with estrogen receptor (ER), progesterone receptor (PR), and HER2/neu-negative (triple-negative) breast tumors [6–9], as well as with tumors of a higher histologic grade [10, 11]. Triple-negative breast cancer has a poorer prognosis than other breast cancers because it is not responsive to targeted anti-hormonal therapies or anti-HER2/neu directed therapies. Additionally, this subtype of breast cancer is associated with faster tumor growth and a higher risk of early recurrence [12, 13], requiring treatment with intensive multi-agent chemotherapy [13, 14].

Numerous prior studies regarding the contribution of SES to racial disparities in overall breast cancer mortality have revealed conflicting results with some studies showing that racial differences in survival persist despite adjustment for sociodemographic factors [15–26], while others indicate that racial disparities can be largely explained by differences in SES [5, 27–35]. We have previously reported on racial disparities in breast cancer survival using a cohort of women diagnosed at a large urban medical center in metropolitan Detroit, reporting that survival differences for AA and white women were largely due to racial disparities in relation to neighborhood-level SES [as defined by a deprivation index (DI)], clinical features, and treatment characteristics [36]. However, fewer studies have examined the influence of SES on the survival of women with specific biological subtypes of breast cancer [6, 11, 17, 37]. SES remains an important variable to study in relation to survival in that it is potentially modifiable and has the potential to affect both access to treatment and attitudes toward care.

In the current analysis, we specifically examined racial differences in survival among a sub-cohort of women with ER and PR-negative breast cancer. We hypothesized that AA and white differences in breast cancer survival would persist among this subset of women with aggressive disease.

Methods

Study sample/data collection

As outlined previously [36], our dataset was created by linking information from three existing databases: Henry Ford Health Systems (HFHS) administrative database, Metropolitan Detroit Cancer Surveillance System (MDCSS), and the U.S. Census Bureau.

HFHS is a network of five hospitals and 36 ambulatory sites within southeast Michigan, located both within the city of Detroit and suburban areas of surrounding Wayne, Macomb, Oakland, and Washtenaw counties. The hospital system collects patient-level information regarding breast cancer subtype, treatments, outcomes, as well as patient comorbidities. The MDCSS encompasses the Surveillance, Epidemiology, and End Results (SEER) registry for the metropolitan Detroit area, which records new cancer diagnoses in southeast Michigan, including patient addresses and corresponding census tracts at the time of diagnosis.

We matched breast cancer records from HFHS with the MDCSS using social security numbers, last names, dates of birth, and medical record numbers. We included in our sample all AA and white women diagnosed with American Joint Committee on Cancer (AJCC) stage I to III ER/PR-negative breast cancer between 1996 and 2005 who had at least 2 months of documented follow-up care at the study institution.

We used 2000 Census data from US Census Bureau data for census-tract level demographic and socioeconomic information in order to create a deprivation index (DI), which is an area-based measure of neighborhood socioeconomic deprivation described below. These data were obtained from US Census Bureau 2000 Summary File 3, Summary Level 140 (Tables H44, H43, P43, H20, and P87, respectively).

Measurement of variables

MDCSS-derived variables included ER/PR status, age at diagnosis, tumor size (classified as <2, 2.1–5, or >5 cm), grade (either well-to-moderately differentiated or poor-to-undifferentiated), and lymph node status. Variables from HFHS included radiation therapy (classified as received or none), and chemotherapy (classified based on type of therapy received). We used the administrative data from HFHS and National Comprehensive Cancer Network (NCCN) (<https://www.nccn.org/>) guidelines for treatment at the time of diagnosis in order to classify chemotherapy specifically as “non-standard adjuvant,” “standard adjuvant,” “neoadjuvant,” or unknown [38]. Data on HER2/neu status were unreliably collected for women diagnosed during the time period of the study, and thus was not available in the HFHS database.

Comorbid medical conditions were quantified with a modified Charlson comorbidity index (CCI), which is a prospectively verified and validated method for assessing the presence of medical conditions that notably affect the risk of mortality in longitudinal studies [39, 40]. CCI was determined from diagnoses in each woman’s HFHS medical record between the year prior and one month after breast cancer diagnosis.

Neighborhood-level SES was calculated using a deprivation index (DI). Our DI used census tract-level data from the 2000 US Census in order to uniquely summarize local economic and social conditions alongside social isolation [38, 41]. The index included the following variables: (1) the proportion of households without a vehicle; (2) the proportion of households without a telephone; (3) the proportion of the population unemployed (>16 years old); (4) the proportion of the population living in a crowded residence (more than 1 person per room); and (5) the proportion of the population living below the poverty line. The composite DI was calculated by adding the value of each of the five variables and dividing

by five to produce a single index value ranging from 0 to 1, with 0 representing no economic deprivation and 1 representing maximal deprivation. The DI was then categorized into quintiles based on the distribution of census tract deprivation within Wayne, Macomb, and Oakland counties (the counties of residence for the vast majority of patients treated at HFHS): quintile 1 (Q1) <0.022, (Q2): 0.022<0.035, Q3:0.035<0.056, Q4: 0.056<0.142, and Q5: 0.142<0.531.

Statistical analysis

Clinical characteristics of AA and white women with ER/PR-negative breast cancer were compared by χ^2 tests. Cox proportional hazards models were used to assess racial differences in survival (including a maximum of 10 year follow-up). Hazard ratios (HR) and 95% confidence intervals (CI) for AA race, age at diagnosis (as a continuous variable), AJCC stage, CCI, DI, radiation therapy, surgical treatment, and chemotherapy were estimated using Cox proportional hazards models. The individual effect of each variable was evaluated in an unadjusted model and then within four variably adjusted models. The first model was adjusted for the effects of clinical variables (age, AJCC stage, and CCI) and race. The second model was adjusted for DI and race. The third model was adjusted for treatment variables (radiation therapy and chemotherapy) and race. The final model was fully adjusted for all the previously mentioned variables. We tested and confirmed the proportional hazards assumption in the final model by adding an interaction term for each variable with the follow-up time. All statistical tests were 2-sided and computed at a 5% significance level (SAS 9.3; SAS Institute, Cary, NC).

Results

From our initial dataset of 2387 women (33% AA) with AJCC Stages I through III breast cancer treated at HFHS between 1996 and 2005, 542 women with ER/PR-negative tumors (45% AA) were included in this analysis. Table 1 provides clinical and demographic characteristics of our cohort by race. Compared to white women, AA women were significantly more likely than whites to have larger tumors (13 vs. 7% > cm, $p = 0.01$), to have a higher CCI (37 vs. 25% with 1 or more comorbid conditions, $p = 0.0069$) and to reside in a more economically deprived area (46 vs. 4% residing in Quintile 5, $p < 0.0001$). There were no significant racial differences in age at diagnosis, tumor grade, involvement of axillary lymph nodes, and receipt of radiation therapy. White women were more likely to have received an unknown type of chemotherapy.

Table 2 shows the results of three models comparing the adjusted predictors of overall survival for AA and white women with breast cancer. In the unadjusted analysis, AA women demonstrated significantly greater overall risk of death compared to white women [hazard ratio (HR) 1.47, 95% confidence interval (CI) 1.09–2.00]. Following multivariate adjustment for clinical factors (age, stage, and CCI), AA race continued to have a significant impact on mortality (HR 1.51, CI 1.10–2.08). Similarly, AA race adversely affected survival after adjustment for receipt of radiation and chemotherapy (HR 1.63, CI 1.20–2.21). However, after adjusting for societal factors alone (DI), race no longer demonstrated a significant association with overall survival (HR 1.26, CI 0.84–1.87).

Discussion

Approximately 20% of women with breast cancer in the US have ER/PR-negative disease, and triple-negative breast cancer is more common among AA women compared with white women [7]. Hence, we sought to examine racial disparities specifically among women with more aggressive, ER/PR-negative breast cancers. Similar to our prior study of racial differences in survival among all types of breast cancer [36], mortality among AA women was greater than that seen among whites, even among the subset of women with the worst prognostic type of breast cancer included in this analysis. AA women notably presented with larger ER/PR-negative tumors and had higher 10-year mortality compared to whites in our unadjusted analysis. Additionally, AA women in our study also bore a greater burden of socioeconomic deprivation and medical comorbidities, suggesting inherent disadvantages in achieving adequate treatment.

Most importantly, in our adjusted analyses, sociodemographic factors (represented by DI) appeared to account for all of the racial differences in survival, which is consistent with the findings of numerous other investigations [5, 27–35]. This suggests that SES may be the primary mediator of racial disparities in breast cancer outcomes. As SES likely has an inherent influence on individual attitudes and access to health care, it has the potential to affect outcomes among all women with breast cancer, including women with ER/PR-negative disease. SES is therefore an important target for public health interventions.

In our analysis, treatment alone failed to explain racial differences in survival as we demonstrated previously [36]. This could be explained by the uniform treatment guidelines imposed at a single, health system from which our study population was established. With shared physicians, dosing regimens, and medical record systems, the hospital system could more easily standardize management across all patients.

Strengths of our analysis include the exclusive focus on women with ER/PR-negative disease, the use of a large well-established cohort of women from a urban medical center, long follow-up time, and use of a validated measure of SES that takes into account multiple variables (such as access to a car, telephone, and household crowding) that could all have a direct adverse impact on access to health care resources [38, 41]. The measure of DI utilized in our study has the potential to reveal forms of deprivation that create major barriers to receipt of health care that have not been captured in prior analyses [15–26].

A primary weakness of our analysis is its lack of information on HER2/neu status, which was not included in the HFHS dataset. The cases included in our analysis occurred between 1996 and 2005, which was prior to the American Society of Clinical Oncology guidelines on standardized HER2/neu testing that were released in 2007 [42]. Nonetheless, ER/PR-negative tumors still demonstrate a more aggressive phenotype compared to receptor-positive tumors, and only 15–20% of all breast cancer cases are HER2/neu positive [43]; thus, our ER/PR-negative cases remain a useful surrogate for women with “triple negative” (ER/PR/HER2/neu negative) tumors. In addition, our focus on data from single health system in southeastern Michigan may limit generalizability to more rural areas with less pronounced socioeconomic deprivation than Detroit.

In conclusion, AA women with ER/PR-negative breast face higher mortality compared to white women, due largely to socioeconomic deprivation. Attempts should be made to understand and remedy socioeconomic barriers to healthcare, since these factors are potentially modifiable and uniquely place both AA and white women at risk for poor outcomes with aggressive breast cancers.

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Table 1

Select clinical characteristics of women diagnosed with hormone-negative invasive breast cancer (AJCC stage I–III) at a single institution by race

	White		African American		<i>p</i> value ^a
	<i>N</i>	%	<i>N</i>	%	
Total	298		244		
Age at diagnosis					0.79
<40	29	9.7%	25	10.2%	
40–49	70	23.5%	55	22.5%	
50–64	95	31.9%	89	36.5%	
65–79	83	27.9%	61	25.0%	
80	21	7.0%	14	5.7%	
Tumor size					0.01
2 cm	156	52.3%	102	41.8%	
2.1–5 cm	105	35.2%	102	41.8%	
>5 cm	21	7.0%	31	12.7%	
Unknown	16	5.4%	9	3.7%	
Grade					0.62
Well-to-moderately differentiated	53	17.8%	40	16.4%	
Poorly differentiated or undifferentiated	232	77.9%	196	80.3%	
Unknown	13	4.4%	8	3.3%	
Lymph node status					0.17
Negative	200	67.1%	150	61.5%	
Positive	98	32.9%	94	38.5%	
Modified Charlson comorbidity index					0.0069
None	205	68.8%	153	62.7%	
1	56	18.8%	60	24.6%	
2	13	4.4%	10	4.1%	
3	6	2.0%	19	7.8%	
Unknown	18	6.0%	2	0.8%	
Deprivation index					<.0001
Quintile 1 (lowest)	86	28.9%	2	0.8%	

	White		African American		<i>p</i> value ^a
	<i>N</i>	%	<i>N</i>	%	
Quintile 2	66	22.1%	11	4.5%	0.03
Quintile 3	86	28.9%	19	7.8%	
Quintile 4	46	15.4%	100	41.0%	
Quintile 5	13	4.4%	112	45.9%	
Unknown	1	0.3%			
Chemotherapy					0.78
None	91	30.5%	68	27.9%	
Neoadjuvant	13	4.4%	16	6.6%	
Adjuvant, non-standard ^b	50	16.8%	45	18.4%	
Adjuvant, standard ^b	112	37.6%	105	43.0%	
Adjuvant, agents unknown	32	10.7%	10	4.1%	0.78
Radiation therapy					
No	92	30.9%	78	32.0%	
Yes	206	69.1%	166	68.0%	

^a *p* value calculation does not include unknown values

^b Based on National Comprehensive Cancer Network guidelines

HRs and 95% CIs of 10-year survival among women with ER/PR-negative breast cancer adjusted by clinical, societal and treatment factors

Table 2

	Clinical factors		Societal		Treatment	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
African American race	1.51 (1.10–2.08)	0.01	1.26 (0.84–1.87)	0.26	1.63 (1.20–2.21)	0.0019
Age at diagnosis	1.03 (1.02–1.04)	<.0001				
AJCC stage	1.75 (1.40–2.19)	<.0001				
Comorbidity index	1.23 (1.03–1.47)	0.02				
Deprivation index			1.09 (0.94–1.27)	0.24		
Radiation					0.64 (0.47–0.88)	0.0054
Chemo, non-standard ^a					0.95 (0.61–1.47)	0.81
Chemo, standard ^a					0.52 (0.35–0.78)	0.0016
Chemo, unknown agents ^a					1.97 (1.25–3.12)	0.0037
Chemo, NeoAdjuvant ^a					1.56 (0.83–2.94)	0.17

^aBased on National Comprehensive Cancer Center guidelines