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Racial disparities in all-cause mortality among younger commercially insured women with incident metastatic breast cancer

Christine Leopold¹, Anita K. Wagner¹, Fang Zhang¹, Christine Y. Lu¹, Craig Earle², Larissa Nekhlyudov^{1,3}, Dennis-Ross Degnan¹, and J. Frank Wharam¹

¹Department of Population Medicine / Drug Policy Research Group, Harvard Medical School and Harvard Pilgrim Health Care Institute

²Health Service Research, Ontario Institute for Cancer Research

³Department of Medicine, Brigham & Women's Hospital, Boston, MA

Abstract

PURPOSE: Racial disparities in breast cancer mortality persists and are likely related to multiple factors. Over the past decade, progress has been made in treating metastatic breast cancer, particularly in younger women. Whether disparities exist in this population is unknown.

METHODS: Using administrative claims data between 2000 and 2011 (OptumInsight, Eden Prairie, MN) of members insured through a large national US health insurer, we identified women aged 25 to 64 years diagnosed with incident metastatic breast cancer diagnosed between November 1, 2000 and December 31, 2008. We examined time from diagnosis to death, with up to 3 years of follow-up. We stratified analyses by geocoded race, and socioeconomic status, age at diagnosis, morbidity score, US region of residence, urban/non-urban, and years of diagnosis. We constructed Kaplan-Meier survival plots and analyzed all-cause mortality using multivariate Cox proportional hazard models.

RESULTS: Among 6694 women with incident metastatic breast cancer (78% Caucasian, 4% African American, and 18% other), we found higher mortality rates among women residing in predominantly African American versus Caucasian neighborhoods (hazard ratio, HR: 1.84; 95% confidence interval, CI: 1.39–2.45), women with high versus lower morbidity (HR: 1.30 [1.12–1.51]), and women whose incident metastatic diagnosis was during 2000–2004 versus 2005–2008 (HR: 1.60 [1.39–1.83]). Caucasian (HR: 0.61 [0.52–0.71]) but not African American women (HR not significant) experienced improved mortality in 2005–2008 versus 2000–2004.

CONCLUSIONS: Despite insured status, African American women and women with multi-morbidity had poorer survival. Only Caucasian women had improved mortality over time. Modifiable risk factors for increased mortality need to be addressed in order to reduce disparities.

Corresponding author: Christine Leopold, PhD, MS; Department of Population Medicine / Drug Policy Research Group, Harvard Medical School and Harvard Pilgrim Health Care Institute, Landmark Center, 401 Park Drive Suite 401, Boston, MA 02215, phone: (617)-867-44813, fax: (617)-867-44276, christine_leopold1@hphc.org.

DISCLOSURE:

Dr. Wagner and Dr. Ross-Degnan did consultancy work for IMS Consulting Group. All other authors have no conflicts to declare.

Keywords

metastatic breast cancer; racial; disparities; mortality; claims data

INTRODUCTION

Breast cancer is among the leading causes of death of US women with an estimated 40,450 deaths in 2016 and a 5-year survival rate of 91% after any breast cancer diagnosis [1–4]. There are 246,660 new cases of breast cancer per year. Approximately 6–10% of patients with breast cancer have metastases at diagnosis and 30–40% will eventually develop metastatic disease [5–8]. The overexpression of the human epidermal growth factor receptor 2 (HER2/neu), which occurs in 20–25% of breast cancer patients, is a risk factor for metastatic breast cancer (mbc) and an indication for treatment with targeted therapies such as trastuzumab [9–12]. However, metastatic breast cancer is incurable and about 50% of patients have disease progression within one year of treatment for advanced disease [13,14].

Racial disparities in breast cancer have been widely documented. Breast cancer incidence increased from 2008 to 2012 among African American women such that rates of diagnosis for African American and Caucasian women converged for the first time in 2012 [15]. Unfortunately, the disparity in breast cancer mortality continued to widen; in 2012 breast cancer death rates were 42% higher among African American than Caucasian women [15]. Compared to Caucasian women, African American women have a higher tumor grade and stage as well as younger age-at-diagnosis [16], and a greater risk of recurrence [17,18]. These differences have been associated with biological and non-biological factors. Biological factors include plasma levels of growth factors and hormones, reproductive patterns, and primary tumor characteristics such as the presence and expression of steroid and growth factor receptors [19–21]. Non-biological differences include lack of screening, delays in diagnosis and access to treatment; treatment modalities used and available; psychological, behavioral, and cultural factors; socioeconomic status (SES), and comorbidities [22–25].

African American women are also more likely to develop late stage and metastatic breast cancer [18,26] often leading to higher mortality. Aizer *et al.* showed that racial discrepancies in mortality persisted between 1998 and 2007 with an increasing gap between African American and Caucasian breast cancer patients [27]. However, the vast majority of studies of mortality disparities among women with metastatic breast cancer have assessed elderly Medicare patients [28,29]; little is known about disparities in mortality among younger (below age 65). Further, whether disparities persist in insured populations is not known.

We examined the effect of racial disparities in all-cause mortality among a large, population-based cohort of younger commercially insured women with incident metastatic breast cancer.

METHODS

Data source

This study used enrollment information and administrative claims data from the Optum® Database (OptumInsight, Eden Prairie, MN) between November 1, 2000 and December 31, 2011, data drawn from a large national health insurer with members in all 50 US states. We linked socio-demographic variables derived from the 2000 US census using census block group of residence. The data vendor linked month and year of death from the Social Security Administration's Death Master files to members in our cohort [30].

Study population

We used a validated definition by Hurvitz *et al.* [31] of metastatic breast cancer in health insurance claims data to identify our sample. The denominator population of patients with metastatic breast cancer was drawn from women aged 25 to 64 with at least two diagnoses of "secondary malignant neoplasm" (International Classification of Diseases, Ninth Revision codes, ICD-9, 197.xx and 198.xx) between November 1, 2000, and December 31, 2008 on separate days but fewer than 91 days apart. To ensure capture of a population with incident metastatic disease, we required that these women have at least six months of enrollment before the first diagnosis of "secondary malignant neoplasm" and defined the first occurrence of this diagnosis as the disease index date. To capture a cohort with metastatic breast cancer, we required at least two independent diagnoses of breast cancer (ICD-9 codes 174–174.9, 233.0) during the 365-day period prior to the disease index date or at least one diagnosis during the 365 days before and at least one within 90 days after the disease index date. From this group, we excluded women diagnosed with other cancer types (excluding non-melanoma skin cancer) prior to the first breast cancer diagnosis claim [31] given uncertainty regarding which of the cancer diagnoses was metastatic. Figure 1 displays the cohort selection flow and relevant sample sizes.

Outcomes measures

The outcome of interest was time (in months) from the metastatic breast cancer disease index date (i.e., incident metastatic breast cancer diagnosis) to all-cause death, with up to 3 years of follow-up after this date.

Covariates and stratifying variables

We evaluated the following predictors of all-cause death: geocoded neighborhood race composition, age-at-diagnosis, comorbidity score (ACG, version 10.0.1) [32,33], geocoded socio-economic status (SES), US region of residence, urban/non-urban residence, and time period of diagnosis. Women were classified as residing in predominantly Caucasian or African American neighborhoods on the basis of living in census block groups with greater than 66% of residents of the given race. The category "mixed" neighborhood composition included women not living in predominantly Caucasian or African American neighborhoods or those with Hispanic or Asian surnames (provided by the data vendor). We classified age-at-diagnosis into 25 to 39, 40 to 49, and 50 to 64 years. To generate proxy measures of SES, previously established [34] categorical variables of census block group poverty and

education levels derived from 2000 US Census reports were created [35]. Women were then classified as from low SES neighborhoods if they lived in census block groups with low education (more than 25% of households with less than high school education) or low income (more than 10% of households below poverty level). Further, during the 6 months preceding the disease index date, women were classified as having low morbidity if their morbidity score (Johns Hopkins ACG® System comorbidity score; ACG, version 10.0.1) was below 3.0 and high morbidity if the ACG score was 3.0 or above. The ACG score was developed on a standardized population in which a score of 1.0 represents average health [32,33]. Women were also categorized by the region of the country in which they resided (Northeast, South, West, and Midwest) on the basis of their most recent zip code. Urban/non-urban area classification was based on members' most recent zip code linked to the US Department of Agriculture commuting area codes [36]. The urban group comprised women living in large metropolitan areas of 1+ million residents and non-urban included all remaining women (urban influence codes 2–12). Finally, members were categorized as having been diagnosed earlier (2000 to 2004) or later (2005 to 2008) based on the calendar year of their disease index date.

Statistical analysis

We used multivariate Cox regression models to generate hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the independent associations of the covariates above with survival (defined as months from disease index date until death) [37]. We displayed time-to-death using Kaplan-Meier survival plots. Maximum follow-up time was 36 months and patients were censored when they turned 65, disenrolled, died or reached end of follow-up, whichever date came first. Statistically significant differences in hazard ratios across categories of a predictor covariate in the Cox regression models were defined as disparities. Our primary predictor of interest was neighborhood race composition. After examining results, we also performed a *post hoc* analysis examining the interaction of neighborhood racial composition and time period of diagnosis to determine if mortality disparities between women from African American versus Caucasian neighborhoods increased over time. All analyses were conducted using SAS (model 9.3). The research protocol was approved by the Harvard Pilgrim Health Care institutional review board.

RESULTS

The cohort comprised 6694 women with incident metastatic breast cancer. Seventy-eight percent (n = 5234, Table 1) were from predominantly Caucasian neighborhoods and 4% (n = 259) were from predominantly African American neighborhoods; 56% (n = 3768) were age 50 to 64 at diagnosis, 31% lived in low SES neighborhoods (n = 2051), most had low morbidity (76%, n = 5096). Forty-one percent of women lived in the South (n = 2769), 69% resided in urban areas (n = 4510), and nearly half of women (48%, n = 3223) were diagnosed with metastatic breast cancer between 2000 and 2004.

3-year overall survival

Table 1 displays unadjusted mortality rates during 3-year follow-up, Table 2 summarizes adjusted hazard ratios from the multivariate Cox model of overall survival, and Figures 2, 3

and 4 display Kaplan-Meier plots of survival by select predictor. Thirteen percent of women (n = 884) died within three years of their first metastatic breast cancer diagnosis. Twenty-three percent and 13% of women from predominantly African American and Caucasian (reference group) neighborhoods, respectively, died during follow-up (African American vs. Caucasian adjusted hazard ratio, HR: 1.84; 95% confidence interval, CI: 1.39–2.45). Fifteen percent of women with high morbidity and 13% of women with low morbidity (reference group) died (HR: 1.30; 95% CI: 1.12–1.51). Nine percent of women living in the Northeast died during follow-up compared with 14% of women living in the South (reference group; HR: 0.73; 95% CI: 0.56–0.95). Corresponding mortality rates among women whose cancer was diagnosed during 2000–2004 versus 2005–2008 (reference group) were 16% and 10% (HR: 1.60; 95% CI: 1.39–1.83), respectively. Our *post hoc* analysis revealed that mortality among women from Caucasian neighborhoods significantly improved for women diagnosed between 2005 to 2008 as compared to women diagnosed between 2000 to 2004 (10% versus 15.5%; 2000–2004 reference group: HR: 0.61; 95% CI: 0.52–0.71) while corresponding mortality rates among women from African American neighborhoods were 21.7% and 23.5% (HR and CI were not significant), respectively. The interaction of neighborhood race and time period was not significant (p=0.15). A Kaplan-Meier plot of this post hoc analysis is displayed in Figure 4.

DISCUSSION

In this population-based cohort of nearly 6700 younger commercially insured women with incident metastatic breast cancer, residence in predominantly African American neighborhoods was strongly correlated with earlier mortality compared with residence in predominantly Caucasian neighborhoods. In addition, women diagnosed between 2000–2004 had substantially higher mortality than women diagnosed between 2005–2008. We found survival disparities with respect to morbidity (high morbidity women had earlier mortality than low morbidity) and geographic region (Northeast lower than South). Importantly, mortality decreased significantly for Caucasian women who were diagnosed between 2005–2008 versus 2000–2004, but not for women from predominantly African American neighborhoods.

Our results were generally similar to previous studies of elderly breast cancer patients, but also contained several important differences in a cohort of younger commercially insured patients. As in studies among older women with metastatic breast cancer [38–41], we found improvement in overall survival over the recent decade (2000–2011) among younger commercially-insured women. General consensus is that mortality has decreased due to the widespread availability of targeted therapies such as trastuzumab for women with HER2-positive disease [42]. Survival disparities by race among younger women are also similar to those documented in earlier studies of older women [43–45]. Several biological factors (such as aggressive histopathology, larger tumor size at presentation, greater nodal involvement, and negative estrogen receptor status) and non-biological factors (such as access to screening and care) have been cited as reasons for differential survival. As shown by the registHER study and a study by Ooi *et al.*, African American breast cancer patients are more likely to have ER/PR-negative and triple-negative tumors than European American and non-Hispanic white breast cancer patients [23,46], and no targeted therapies are available for these

patients. Also similar to previous studies [47–50], we found that high morbidity was associated with higher mortality among women with metastatic breast cancer. Further, our findings regarding geographic disparities with better overall survival for women living in the Northeast as compared to living in the South mirror findings by DeSanit *et al.*, who showed that death rates decreased faster in the Northeast as compared to the South during the timeframe 1975 to 2004 [51]. A second study DeSanit *et al.* detected a striking worsening in long-term mortality trends among African American compared with Caucasian women [15]. Our study of younger commercially insured women confirms this divergence: Caucasian but not African American women experienced substantial increases in survival between 2000–2004 and 2005–2008. It is possible that differential HER2-positive status between African American and Caucasian women, compounded by differential access to effective therapies such as trastuzumab, might explain differences in survival over time.

Unlike studies that used Medicare SEER data and detected survival disparities by income level among older women [52–54], we did not find that low SES predicted worse outcomes. Although the reasons for this different finding are unclear, it is possible that lower SES women who are younger and commercially insured have better access to screening and care than older, Medicare insured women with lower SES. Another reason could be that effective therapies such as trastuzumab may be less commonly offered to older women with pre-existing heart conditions.

We acknowledge several limitations of this study. First, our findings are associational and we cannot make inferences about causes of mortality disparities among women with metastatic breast cancer. Second, we did not have access to screening patterns prior to diagnosis and pathology and laboratory results that could provide information about breast cancer subtypes and hormone receptor status. Third, we could not capture other potentially important predictors of survival such as reproductive patterns or physical health and diet. In addition, despite our large sample size, our study was not powered to analyze interactions between race and other predictors such as residence in a rural area or very low-income neighborhood. The small sample size of African American women likely limited our ability to detect a statistically significant difference in mortality between African American and Caucasian women over time. Finally, the census-based neighborhood characteristics we used could lead to some misclassification of women, but these variables have been validated [25] and also characterize neighborhood characteristics (such as access to local facilities) that are not captured by member-level variables.

In conclusion, we found disparities in survival by race, morbidity, and US region of residence in a cohort of younger commercially insured women with incident metastatic breast cancer. Further, Caucasian but not African American women had improved mortality over time. While differences in mortality may be based on biological and treatment factors, modifiable risk factors must be addressed. Policy makers, health plans and clinicians should consider approaches to provide timely treatment and support to women presenting with metastatic breast cancer, particularly targeting African American women and women living in potentially vulnerable geographical areas of the U.S.

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Figure 1: Definition of metastatic breast cancer cohort

BC = breast cancer, N= number, SM = secondary malignant

Source: adjusted from [31]

— African American	259	235	216	200
— Caucasian & mixed	6421	6057	5786	5615

Figure 2: 3-year survival stratified by race for women age 25–64 with metastatic breast cancer

African American: residing in predominantly African American (66%) neighborhoods

Caucasian: residing in predominantly Caucasian (66%) neighborhoods

Mixed: women with Hispanic or Asian surname as well as women residing in predominantly mixed neighborhoods

Plot shows unadjusted mortality during 3-year follow-up.

Total cohort N = 6680 as 14 are missing

— yr_2000-2004	3223	3006	2842	2714
- - - yr_2005-2008	3471	3299	3171	3112

Figure 3: 3-year survival stratified by year of diagnosis for women with metastatic breast cancer
 Plot shows unadjusted mortality during 3-year follow-up.
 Total cohort N = 6694

— African American_2000-2004	153	139	128	117
- - - African American_2005-2008	106	96	88	83
— Caucasian_2000-2004	2555	2388	2262	2167
- - - Caucasian_2005-2008	2679	2548	2457	2415

Figure 4: 3-year survival stratified by race and year of diagnosis among African American and Caucasian women with metastatic breast cancer

African American: residing in predominantly African American (66%) neighborhoods

Caucasian: residing in predominantly Caucasian (66%) neighborhoods

Mixed: women with Hispanic or Asian surname as well as women residing in predominantly mixed neighborhoods

Plot shows unadjusted mortality during 3-year follow-up.

Total cohort N = 5493 (as mixed (N=1187) are excluded and 14 are missing)

Table 1:

Characteristics of US Women with metastatic breast cancer

Variables	Number (%) of women		Unadjusted mortality during 3-year follow-up, number (%)	
Women	6694	100%	884	13%
<i>Neighborhood racial composition¹ (missing n=14) (missing n=3)</i>				
African American	259	4%	59	23%
Mixed	1187	18%	157	13%
Caucasian	5234	78%	665	13%
<i>Age-at-diagnosis</i>				
25 – 39 years	685	10%	83	12%
40 – 49 years	2241	33%	279	12%
50 – 64 years	3768	56%	522	14%
<i>Socio-economic status (SES)²</i>				
Low SES	2051	31%	302	15%
High SES	4643	69%	582	13%
<i>Morbidity (ACG)³</i>				
High morbidity	1598	24%	243	15%
Low morbidity	5096	76%	641	13%
<i>Geographic region (missing n=5)</i>				
Northeast	716	11%	68	9%
West	851	13%	124	15%
Midwest	2353	33%	308	13%
South	2769	41%	384	14%
<i>Urban/non-urban area⁴ (missing n=147) (missing = 27)</i>				
Non-urban	2037	31%	279	14%
Urban	4510	69%	578	13%
<i>Year of diagnosis</i>				
2000 – 2004	3223	48%	521	16%
2005 – 2008	3471	52%	363	10%

¹ *African American*: residing in predominantly African American (66%) neighborhoods
Caucasian: residing in predominantly Caucasian (66%) neighborhoods

Mixed = women with Hispanic or Asian surname as well as women residing in predominantly mixed neighborhoods

² *Low SES*: > 25% only HS education or > 10% below poverty
High SES: <25% only HS education or <10% below poverty

³ *Very high morbidity*: ACG score > 3.0
Low morbidity: ACG score 0 – 3.0

⁴ *Non-urban*: all remaining categories 2 – 12
Urban: large metropolitan area of 1+ million residents [36]

ACG = Adjusted Clinical Groups, HS = high school, SES = socioeconomic status

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Table 2:

Multivariate analysis of overall survival for women with metastatic breast cancer

Predictors	Total mbc cohort (N=6539)	
	Hazard ratio	95% CI
<i>Ethnicity¹ (reference = Caucasian)</i>		
African American	1.84	1.39–2.45
Mixed	1.04	0.86–1.26
<i>Age-at-diagnose (reference = 50–64 years)</i>		
25–40 years	0.85	0.67–1.07
40–49 years	0.89	0.77–1.03
<i>Socio-economic status² (reference = high SES)</i>		
Low SES	1.05	0.90–1.23
<i>Morbidity³ (reference = low morbidity)</i>		
High morbidity	1.30	1.12–1.51
<i>Geographic region (reference = South)</i>		
West	1.20	0.97–1.48
Midwest	0.95	0.81–1.11
Northeast	0.73	0.56–0.95
<i>Urban / non-urban⁴ (reference = urban areas)</i>		
Non-urban areas	1.09	0.94–1.26
<i>Year of diagnosis (reference = 2005–2008)</i>		
2000–2004	1.60	1.39–1.83

Bold means significant p = <0.05

¹ *African American*: residing in predominantly African American (66%) neighborhoods*Caucasian*: residing in predominantly Caucasian (66%) neighborhoods*Mixed* = women with Hispanic or Asian surname as well as women residing in predominantly mixed neighborhoods² *Low SES*: > 25% only HS education or > 10% below poverty*High SES*: <25% only HS education or <10% below poverty³ *Very high morbidity*: ACG score > 3.0*Low morbidity*: ACG score 0 – 3.0⁴ *Non-urban*: all remaining categories 2 – 12*Urban*: large metropolitan area of 1+ million residents [36]

ACG = Adjusted Clinical Groups, HS = high school, mbc = metastatic breast cancer, SES = socioeconomic status