The Influence of Medical Comorbidities on Survival Disparities in a Multiethnic Group of Patients with *De Novo* Metastatic Breast Cancer

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ABSTRACT

Background: The influence of common medical comorbidities on mortality and racial/ethnic disparities in mortality among women with metastatic breast cancer remains largely unknown.

Methods: In this longitudinal study, women with newly diagnosed stage IV breast cancer were identified in a large, diverse, integrated healthcare delivery system from January 2009 to December 2017 ($n = 995$) and followed through December 31, 2018, for all-cause (overall) and breast cancer–specific mortality via electronic health records. We computed overall and breast cancer–specific mortality rates by race/ethnicity and Elixhauser comorbidity index (ECI). Multivariable-adjusted hazard ratios (HR) assessing the influence of race/ethnicity and comorbidity status on overall and breast cancer–specific mortality were estimated using proportional hazards regression adjusted for age, breast cancer subtype, geocoded income, and palliative cancer treatments.

Results: Nearly 17% of this cohort had diabetes and 45% had hypertension. Overall, 644 deaths occurred in the cohort (median follow-up time of 1.8 years), of which 88% were breast cancer related. The risk of overall mortality was increased in Asian/Pacific Islander (PI; adjusted HR = 1.45; 95% CI, 1.10–1.92) and African American/Black women (adjusted HR = 1.34; 95% CI, 1.02–1.76) when compared with white women. Women with more comorbidities (ECI ≥ 5) had more than 3-fold higher overall mortality rate than those without any comorbidities [602/1,000 person-year (PY) vs. 175/1,000 PY]. Similar associations were found for breast cancer–specific mortality.

Conclusions: Medical comorbidities are associated with an increased risk of overall mortality among women with de novo metastatic disease and may influence racial/ethnic disparities in mortality.

Impact: Optimizing the management of medical comorbidities in metastatic breast cancer patients may also help reduce disparities in breast cancer–related mortality.

Introduction

In the United States, nearly 16,000 women are diagnosed with *de novo* stage IV breast cancer each year (1), and currently 150,000 women are living with metastatic breast cancer. As a result of advances in treatment and early detection, breast cancer mortality rates have been declining over time. However, the improvements in mortality rates have not been equally realized across racial/ethnic groups. African American/Black women are more likely to be diagnosed *de novo* with distant disease and more likely to have unfavorable tumor characteristics, such as triple-negative hormone receptor status when compared with white women. These differences along with other less-readily measurable factors such as the impact of racial bias in care delivery have likely led African American/Black women to experience lower overall survival after diagnosis with metastatic breast cancer when compared with white women (2). In fact, recent registry data collected between 2009 and 2015 suggest that the 5-year metastatic breast cancer–specific survival rate is just 21% among African American/Black women compared with 28% for white women (3). Even less is known about women from other racial/ethnic backgrounds. Many factors may contribute to disparities in breast cancer mortality, including but not limited to socioeconomic status (SES); access to screening and healthcare; tumor biology; implicit providers' bias; differences in disease management and care delivery in various healthcare settings; comorbidity status; lifestyle/behaviors; and environmental exposures.

It is already established that being enrolled in a health insurance plan at the time of diagnosis is strongly associated with better overall survival as well as cancer–specific outcomes such as recurrence and progression-free survival in many broad categories of cancer patients (4–10). Although some recent studies have examined metastatic breast cancer outcomes by both race/ethnicity and SES (11, 12), these included a mix of patients with and without health insurance, making it difficult to disentangle the prominent effects of health insurance coverage from other factors. In addition, although prior studies suggest that medical comorbidities are associated with delay in treatment, increased hospitalizations, and higher mortality in breast cancer patients, these studies have been largely limited to nonmetastatic disease (13–20). Consequently, the prevalence of major comorbidities among women diagnosed with *de novo* stage IV breast cancer remains poorly characterized. The influence of common comorbidities on breast cancer mortality and whether these comorbidities may be contributing to racial/ethnic disparities in survival in this population also remains unknown.

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Given these gaps, the goals of this study were to assess racial/ethnic disparities in mortality risk in a diverse group of women with de novo stage IV metastatic breast cancer who were all insured by a single managed care organization at time of first diagnosis, and to assess the influence of preexisting medical comorbidities and other patient factors on mortality risk.

Materials and Methods

Study design, subjects, and setting

We assembled a cohort of adult women (≥18 years) newly diagnosed with breast cancer (American Joint Committee on Cancer [AJCC] TNM stages I–IV) from January 2009 to December 2017 (n = 30,609). Of these, 995 were staged with metastatic disease (stage IV) at the onset of first diagnosis ("*de novo* metastatic breast cancer") and constituted our study population. These patients were followed via electronic chart review through December 31, 2018 (10 years maximum follow-up time). All patients were members of the Kaiser Permanente Southern California (KPSC) health plan, a not-for-profit integrated healthcare delivery system comprised of 15 community hospitals and 220 medical offices geographically spread across ethnically diverse Southern California, in total serving over 4.7 million members. KPSC patients receive virtually all of their medical care, including pharmacy prescriptions, within this healthcare delivery system. Rare medical procedures and hospitalizations conducted outside of the system and associated diagnoses were captured from claims databases. Members of the study group were identified using the KPSC's NCI's-Surveillance Endpoints and End Results (SEER)-affiliated cancer registry. The study was reviewed by the KPSC Internal Review Board, which waived the right to obtain written or verbal consent from patients for this deidentified analytic data set. Access to the study analytic data set may be requested from the corresponding author. Due to privacy rules and HIPAA regulations, a data use agreement will be needed with Kaiser Permanente; approval by the organization's IRB; and potential funding to support programming efforts.

Main outcomes

The main outcomes of interest were all-cause (overall) mortality and breast cancer–specific mortality. Patients' records were followed through December 31, 2018, regarding vital status. Breast cancer deaths were ascertained by the underlying causes of death using the International Classification of Disease 10th Revision (ICD-10) code C50. Date of deaths and causes were extracted from three sources and cross-referenced for accuracy: KPHC health plan's inpatient databases, the California state death database, and national death databases based on social security linkages.

Independent variables

Main variables of interest included race/ethnicity (non-Hispanic White; African American/Black; Latina; Asian/Pacific Islander (PI); Other/mixed/Native American). We extracted the most common comorbidities (diabetes, hypertension, and depression) one year before the breast cancer diagnosis from electronic health records, using an electronic algorithm of ICD9CM and ICD10CM codes successfully used in our prior cancer studies. Additional comorbidities were also examined using the Elixhauser comorbidity index (ECI) score, which includes 30 conditions that are weighted based on the association of the conditions with mortality (21).

Covariates

Covariates included age at diagnosis; year of diagnosis; and geocoded median household income (as a measure of SES) based on the U.S. 2010 Census data (22); smoking history, and body mass index (BMI) closest to the initial breast cancer diagnosis. Information on first-course cancer therapy in the first six months post diagnosis, including chemotherapy, was extracted from the SEER registry. The days from cancer diagnoses to start date of first-course treatment were calculated. We also captured intrinsic subtype based on the combination of estrogen (ER), progesterone (PR), and HER-2 markers (triple-negative, luminal A, luminal B, HER-2 enriched), grade, and tumor size.

Statistical analysis

Descriptive statistics of demographics and tumor characteristics by race/ethnicity were first examined in frequencies and proportion for categorical variables using chi-square test or Fisher exact test. Time to treatments was evaluated via median and interquartile range using Kruskal–Wallis test for nonnormally distributed data. Follow-up time was started from the breast cancer diagnosis date and ended on the date of death, or study's end on December 31, 2018, whichever occurred first. Because patients had varying follow-up lengths based on time of diagnosis, we calculated person-year (PY) mortality rates and 95% confidence intervals by race/ethnicity based on person-time at risk as denominator.

Multivariable adjusted hazard ratios (HR) for the association between overall mortality and race/ethnicity adjusted for covariates were then estimated using Cox proportional hazards models accounting for the aforementioned covariates. The same analytic techniques were used to examine breast cancer–specific mortality based on separate Cox proportional hazards models. Final models were selected based on the clinical importance, combination of goodness of fit, and assessment of collinearity among covariates. The variables in the model were assessed for collinearity and were maintained if the variance inflation factor was <2.5 or the correlation coefficient was <0.5. The proportional assumption was tested via graphic plots and residual analysis. Less than 4% of the main confounders (e.g, geocoded income; BMI) were missing; therefore, missing values were handled as an additional category in all models. This was decided based on a complete-case assessment, restricting the analysis to individuals with no missing covariate data, which yielded unchanged results. We then stratified the multivariable adjusted Cox models estimating the associations of race/ethnicity with mortality (both all-cause and breast cancer specific) by comorbidity status (for both the individual conditions and the ECI score).

In another model, we used a propensity score analysis to better balance covariates for palliative chemotherapy because this therapy was strongly associated with patient characteristics. The probability of exposure (propensity score) was estimated for each patient using a multivariable logistic regression model, in which chemotherapy use status was regressed on observed baseline characteristics. The inverse probability of treatment weight (IPTW) was calculated using the propensity score for each subject, then normalized (23). We developed the Cox proportional hazards model with the IPTW to assess the mortality risk associated with palliative chemotherapy for the overall and breast cancer–specific mortality. Standardized difference scores were used to assess whether balance of covariates was achieved between the comparison groups. Separate models were created to estimate the adjusted risk of overall and breast cancer–specific mortality. All analyses were performed using SAS 9.4 (SAS Institute Inc).

Results

Baseline demographic and clinical characteristics are displayed in **Table 1**. Of the 995 women in our sample, 52% were non-Hispanic white; 14% were African American/Black; 20% were Latina; 11% were Asian/PI; and 3% were of other/mixed/Native American race/ethnicity. The baseline characteristics (age; geocoded income; comorbidities, BMI, smoking) all varied significantly by race/ethnicity (all $P < 0.001$). Compared with white women, a greater proportion of African American/Black women were in the lower SES group (≤$40,000 annual geocoded median household income). African American/Black women also had a substantially greater burden of common comorbidities including obesity (45% at BMI ≥ 30 kg/m^2), diabetes (25%), and hypertension (64%) when compared with white women. In fact, 32% of African American/Black patients demonstrated ECI ≥ 5 at time of metastatic breast cancer diagnosis, compared with just 19% of white women. Among Hispanic patients, the prevalence of these comorbidities was the second highest: diabetes (20%); hypertension (38%); and BMI ≥ 30 kg/m^2 (42%). Breast cancer subtypes also varied by race/ethnicity ($P < 0.001$); Latina patients were more likely than white patients to have Luminal B and HER-2 enriched tumors. Latina and Asian/PI women were slightly younger when diagnosed with *de novo* metastatic breast cancer, and more likely to have diabetes than their white counterparts.

Table 2 presents the distribution of cancer treatments and time to treatment by race/ethnicity. The majority of women in did not undergo primary surgery (69%) or palliative radiotherapy (80%). However, women of color were similarly likely to undergo palliative radiotherapy ($P = 0.97$) and use hormonal therapy ($P = 0.26$) as compared with their white counterparts. Women of color [African American/Black (50%); Hispanic (72%), Asian/PI (68%), and other/mixed/Native American (59%)) were similarly or more likely to undergo chemotherapy than white women (53%; $P < 0.001$). Only a small proportion of the overall cohort received immunotherapy (8%), and differences on this domain were not analyzed further due to small numbers. Regarding median time to treatment, the median time to palliative therapies did not vary by race/ethnicity ($P > 0.25$ for all treatments; **Table 2**).

Overall, there were 644 deaths among the 995 women of this cohort, of which 568 (88.2%) were deemed to be breast cancer–related deaths. The crude overall mortality rate was 255/1,000 PY, and 225/1,000 PY for breast cancer–specific mortality. **Figure 1** shows the mortality PY rates by comorbidity status, stratified by race/ethnicity. Overall, mortality rates were highest for African American/Black women, followed by Asian/PI, white, and lowest for Hispanic women. Interestingly, the overall mortality rates increased with increasing ECI score for all race/ethnicities; those with an ECI ≥ 5 had more than 3-fold higher rate than those without any comorbidities across all race/ethnicities, and this was most pronounced among White, African American/Black and Asian PI women. Among White, African American/Black and Asian/PI women, those with diabetes had consistently greater mortality rates than those without, but similar rates were seen among Latinas. Women with hypertension had greater mortality rates when compared with those without hypertension, among Asian/PI women only (**Fig. 1**).

Figure 2A displays the multivariable adjusted results for overall mortality. Compared with white patients, the risk of overall mortality was greater in African American/Black women (adjusted HR = 1.34; 95% CI, 1.02–1.76 and Asian/PI women (adjusted HR = 1.45; 95% CI, 1.10–1.92) after accounting for age at diagnosis, year of diagnosis, geocoded income, ECI, and cancer treatments. Interestingly, the overall mortality risk progressively increased with increasing ECI (P for trend <0.001). For example, those with ECI = 4 had a 44% increased mortality risk (HR = 1.44; 95% CI, 1.05–1.97) and for those with ECI ≥ 5, the mortality risk was over 2-fold greater (HR = 2.12; 95% CI, 1.59–2.82) compared with women with no comorbidities (ECI = 0).

Figure 2B shows breast cancer–specific mortality. We observed a statistically significant increase in risk of breast cancer mortality in Asian/PI women (adjusted HR = 1.40; 95% CI, 1.03–1.89) compared with white patients. We also observed a slightly increased, but not statistically significant, risk of breast cancer mortality in African American/Black women (HR = 1.30; 95% CI, 0.98–1.73), compared with white women. Women with other/mixed/Native American backgrounds had 2.8-fold increased risk of breast cancer mortality (adjusted HR = 2.87; 95% CI, 1.71–4.80), but these data were based on a smaller number of deaths ($n = 16$). As above, we observed a greater risk of breast cancer–specific deaths with increasing ECI scores (P for trend = 0.003). For example, women in the highest category, ECI ≥ 5, were nearly 2-fold (adjusted HR = 1.91; 95% CI, 1.41–2.59) more likely to die of breast cancer than those without any comorbidities. As expected, due to hormone receptor–based treatment limitations, and other unknown biological factors yet to be defined, women with triple-negative breast cancer also had an increased breast cancer mortality risk (adjusted HR = 2.04; 95% CI, 1.50–2.77).

Table 3 displays the multivariable adjusted results for overall and breast cancer–specific mortality, stratified by comorbidity status and ECI score. When stratified by the individual comorbidities and ECI score, no clear patterns of effect modification were seen for either of the mortality outcomes. However, among African American/Black women, the risks of both overall and breast cancer–specific mortality were lower among those with one of the four common comorbidities or greater ECI scores, suggesting that the association of race/ethnicity with mortality was in part attenuated by accounting for comorbidities. Similar patterns of attenuation of the association between race/ethnicity and mortality were seen across the other racial/ethnic groups, most notably when stratifying by diabetes and depression (**Table 3**).

Supplementary Table S1 presents the proportion of women who received chemotherapy by ECI score. Receipt of chemotherapy decreased with increasing ECI score; only 34% of women with five or more comorbidities received chemotherapy, compared with 73% of those with no comorbidities ($P < 0.001$).

Supplementary Table S2 presents the risks of overall and breast cancer–specific mortality by palliative chemotherapy. Using Cox proportional hazards models incorporating propensity score of IPTW, palliative chemotherapy was statistically significantly associated with a reduction in risk of overall mortality as well as metastatic breast cancer–specific mortality. For overall mortality, the results of palliative chemotherapy from the Cox proportional hazards model (adjusted HR = 0.44; 95% CI, 0.36–0.55) and from the model based on IPTW propensity scores (adjusted HR = 0.60; 95% CI, 0.50–0.71) were somewhat similar, demonstrating absolute benefit (versus no chemotherapy). This risk reduction was similar for breast cancer–specific mortality.

Discussion

In this diverse, large sample of similarly insured women diagnosed with *de novo* metastatic breast cancer, the multivariable-adjusted risks of overall and breast cancer–specific mortality varied by race/ethnicity, with greater risks for both outcomes occurring in Asian/PI as well as African American/Black women, even though median time to cancer treatments was generally similar across all racial/ethnic groups.

Table 1. Demographic and clinical characteristics of women with *de novo* stage IV breast cancer diagnosed, stratified by race/ethnicity 2009–2017 ($n = 995$).

	White ($N = 522$) *n* (%)	African American ($N = 139$) *n* (%)	Asian/PI ($N = 110$) *n* (%)	Hispanic ($N = 198$) *n* (%)	Other/Mixed/ Native American ($N = 26$) *n* (%)	Total ($N = 995$) *n* (%)	*P* value
Demographic Characteristics							
Age at diagnosis (years)							<0.001
<40	27 (5.2)	9 (6.5)	9 (8.2)	21 (10.6)	1 (3.9)	67 (6.7)	
40–49	62 (11.9)	23 (16.6)	27 (24.6)	40 (20.2)	5 (19.2)	157 (15.8)	
50–59	104 (19.9)	23 (16.6)	21 (19.1)	46 (23.2)	13 (50.0)	207 (20.8)	
60–69	123 (23.6)	29 (20.9)	30 (27.3)	48 (24.2)	1 (3.9)	231 (23.2)	
70–79	121 (23.2)	32 (23.0)	16 (14.6)	27 (13.6)	4 (15.4)	200 (20.1)	
80+	85 (16.3)	23 (16.6)	7 (6.4)	16 (8.1)	2 (7.7)	133 (13.4)	
Median annual household income							<0.001
≤$40,000	47 (9.3)	55 (40.2)	11 (10.7)	31 (16.2)	2 (8.7)	146 (15.2)	
$40,001–$65,000	170 (33.5)	50 (36.5)	42 (40.8)	88 (46.1)	16 (69.6)	366 (38.2)	
$65,001+	290 (57.2)	32 (23.4)	50 (48.5)	72 (37.7)	5 (21.7)	449 (46.7)	
Missing	15	2	7	7	3	34	
Clinical Characteristics							
Subtypes of breast cancer							<0.001
Luminal A (ER^+ or PR^+ and HER2-)	253 (51.9)	70 (55.6)	50 (49.0)	102 (54.3)	11 (42.3)	486 (52.4)	
Luminal B (ER^+ or PR^+ and $HER2^+$)	60 (12.3)	9 (7.1)	14 (13.7)	32 (17.0)	0 (0)	115 (12.4)	
HER2 enriched (ER^- and PR^- and $HER2^+$)	21 (4.3)	12 (9.5)	10 (9.8)	20 (10.6)	6 (23.1)	69 (7.4)	
HER2 missing and HR^+ (ER^+ or PR^+)	75 (15.4)	13 (10.3)	15 (14.7)	11 (5.9)	4 (15.4)	118 (12.7)	
HER2 missing and HR^- (ER^- and PR^-)	19 (3.9)	7 (5.6)	3 (2.9)	2 (1.1)	2 (7.7)	33 (3.6)	
Triple-negative	59 (12.1)	15 (11.9)	10 (9.8)	21 (11.2)	2 (7.7)	107 (11.5)	
Missing/test(s) not done	35	13	8	10	1	67	
Grade							0.511
1	41 (10.0)	9 (8.1)	2 (2.3)	17 (10.0)	2 (8.7)	71 (8.9)	
2	188 (45.9)	54 (48.7)	39 (44.3)	74 (43.5)	10 (43.5)	365 (45.5)	
3	181 (44.2)	48 (43.2)	47 (53.4)	79 (46.5)	11 (47.8)	366 (45.6)	
Unknown/missing	112	28	22	28	3	193	
Tumor size (cm)							0.078
No mass	12 (2.9)	5 (4.4)	1 (1.2)	1 (0.6)	0 (0)	19 (2.4)	
<1	12 (2.9)	6 (5.3)	1 (1.2)	9 (5.4)	1 (5.0)	29 (3.6)	
1–1.9	57 (13.9)	18 (15.8)	5 (5.8)	18 (10.7)	3 (15.0)	101 (12.7)	
2–2.9	65 (15.9)	9 (7.9)	8 (9.3)	24 (14.3)	0 (0)	106 (13.3)	
3–3.9	73 (17.8)	19 (16.7)	17 (19.8)	27 (16.1)	2 (10.0)	138 (17.3)	
4–4.9	50 (12.2)	10 (8.8)	9 (10.5)	20 (11.9)	2 (10.0)	91 (11.4)	
≥5	141 (34.4)	47 (41.2)	45 (52.3)	69 (41.1)	12 (60.0)	314 (39.4)	
Unknown/missing	112	25	24	30	6	197	
Elixhauser comorbidity index							<0.001
0	125 (23.9)	23 (16.6)	37 (33.6)	52 (26.3)	11 (42.3)	248 (24.9)	
1	89 (17.1)	24 (17.3)	17 (15.5)	52 (26.3)	4 (15.4)	186 (18.7)	
2	100 (19.2)	16 (11.5)	23 (20.9)	28 (14.1)	5 (19.2)	172 (17.3)	
3	61 (11.7)	16 (11.5)	10 (9.1)	25 (12.6)	5 (19.)	117 (11.8)	
4	45 (8.6)	15 (10.8)	9 (8.2)	20 (10.1)	1 (3.9%)	90 (9.1)	
≥5	102 (19.5)	45 (32.4)	14 (12.7)	21 (10.6)	0 (0)	182 (18.3)	
Diabetes	66 (12.6)	34 (24.5)	19 (17.3)	40 (20.2)	6 (23.1)	165 (16.6)	0.005
Hypertension	225 (43.1)	89 (64.0)	44 (40.0)	75 (37.9)	10 (38.5)	443 (44.5)	<0.001
Depression	101 (19.4)	22 (15.8)	5 (4.6)	25 (12.6)	2 (7.7)	155 (15.6)	<0.001
BMI (kg/m^2)							<0.001
<18.5 (underweight)	18 (3.5)	11 (7.9)	1 (0.9)	1 (0.5)	1 (3.9)	32 (3.2)	
18.5–24.9 (healthy)	180 (34.7)	32 (23.0)	55 (50.5)	58 (29.3)	10 (38.5)	335 (33.8)	
25–29.9 (overweight)	146 (28.1)	33 (23.7)	34 (31.2)	56 (28.3)	8 (30.8)	277 (28.0)	
30 or more (obesity)	175 (33.7)	63 (45.3)	19 (17.4)	83 (41.9)	7 (26.9)	347 (35.0)	
Unknown/missing	3	0	1	0	0	4	
Smoking status							<0.001
Current	42 (8.1)	13 (9.4)	6 (5.5)	6 (3.0)	2 (7.7)	69 (6.9)	
Former	107 (20.5)	23 (16.6)	8 (7.3)	20 (10.1)	2 (7.7)	160 (16.1)	
Never	373 (71.5)	103 (74.1)	96 (87.3)	172 (86.9)	22 (84.6)	766 (77.0)	

Table 2. Treatment receipt and time to treatment by race/ethnicity among women with *de novo* stage IV breast cancer diagnosed 2009–2017, $n = 995$.

	White ($N = 522$) *n* (%)	African American/Black ($N = 139$) *n* (%)	Asian/PI ($N = 110$) *n* (%)	Latina ($N = 198$) *n* (%)	Other/Mixed/ Native American ($N = 26$) *n* (%)	Total ($N = 995$) *n* (%)	*P* value[a]
Treatment receipt							
Surgery	159 (30.5)	43 (30.9)	31 (28.5)	67 (33.9)	5 (19.3)	305 (30.7)	0.580
Palliative radiation	109 (20.9)	26 (18.7)	21 (19.1)	42 (21.2)	5 (19.3)	203 (20.4)	0.970
Palliative hormonal therapy	268 (51.3)	58 (41.7)	49 (44.6)	101 (51.1)	13 (50.0)	489 (49.2)	0.260
Palliative chemotherapy	279 (53.5)	70 (50.4)	75 (68.2)	144 (72.7)	18 (69.2)	586 (58.9)	<0.001
Immunotherapy	33 (6.3)	3 (2.2)	11 (10.0)	26 (13.2)	5 (19.2)	78 (7.8)	<0.001
Median time to treatment (days, Q1, Q3)							
Surgery	32 (15, 61)	36 (19, 118)	31 (7, 62)	29 (15, 56)	11 (0, 200)	31 (15, 62)	0.750[b]
Radiation	77 (40, 204)	90 (42, 174)	143 (31, 232)	91 (31, 236)	217 (42, 339)	82 (38, 218)	0.867[b]
Hormonal therapy	50 (23, 118)	51 (27, 115)	54 (24, 143)	65 (32, 162)	96 (35, 200)	54 (26, 126)	0.256[b]
Chemotherapy	40 (23, 75)	42 (24, 84)	44 (24, 66)	43 (26, 77)	29 (20, 44)	41 (24, 73)	0.292[b]
Immunotherapy	43 (27, 99)	81 (27, 135)	59 (38, 107)	36 (20, 71)	63 (28, 129)	43 (27, 81)	0.411[b]

[a]*P* values based on Pearson chi-square test or Fisher exact test, except indicated.
[b]*P* values were calculated using Kruskal–Wallis test.

Women with more comorbid conditions also had a greater risk of overall mortality, after adjustment for race/ethnicity and other covariates. Our findings suggest that racial/ethnic disparities in overall mortality among women with *de novo* metastatic disease are in part influenced by both socioeconomic and cancer-related factors, including the disproportionate burden of noncancer comorbidities.

Our study is the first to our knowledge to suggest the risk of overall and breast cancer–specific mortality increases with increasing comorbidity (ECI) scores among women with metastatic breast cancer. Prior studies suggest the majority of women diagnosed with breast cancer have one or more preexisting comorbid conditions, and that comorbid diabetes, hypertension, and obesity are associated with poorer overall survival and disease-specific survival among women with all stages of breast cancer (1, 16, 18, 24). Our findings suggest that this is also the case for women specifically diagnosed with metastatic breast cancer, and that differential comorbidity burden may be in part contributing to the racial/ethnic disparities in mortality seen among this population.

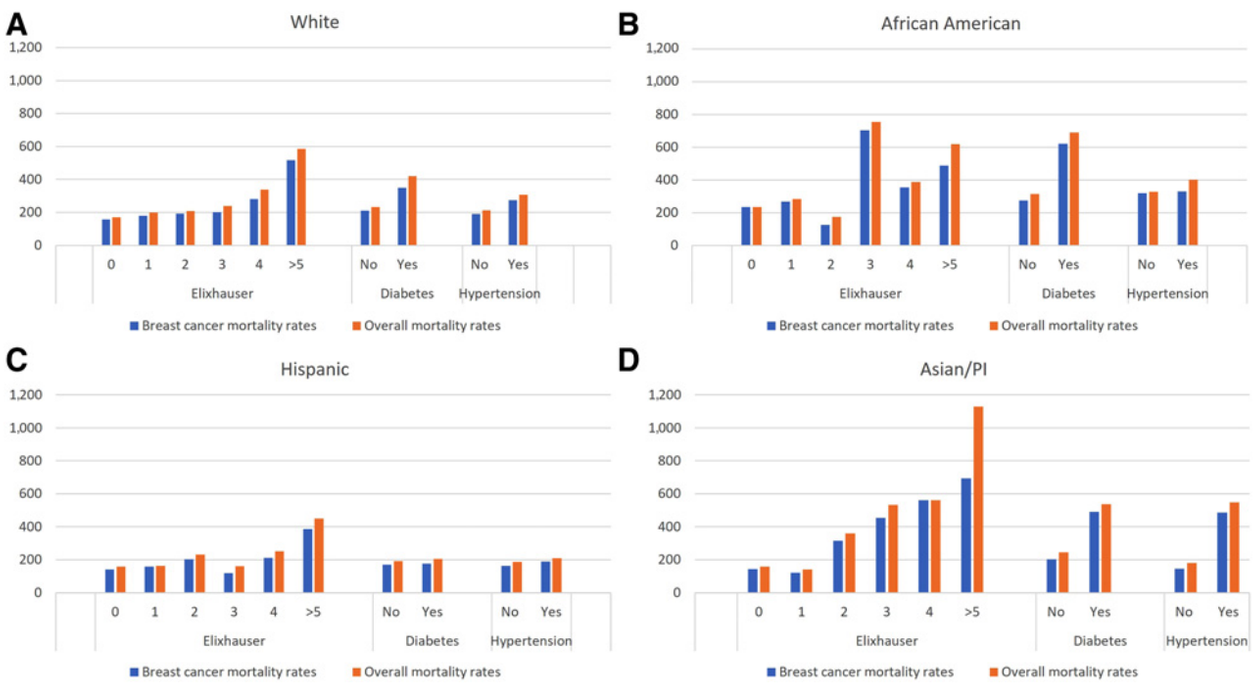

Figure 1.
Crude mortality rates by comorbidity status, stratified by race/ethnicity (**A**) white, (**B**) African American/Black, (**C**) Latina, and (**D**) Asian/Pacific Islander.

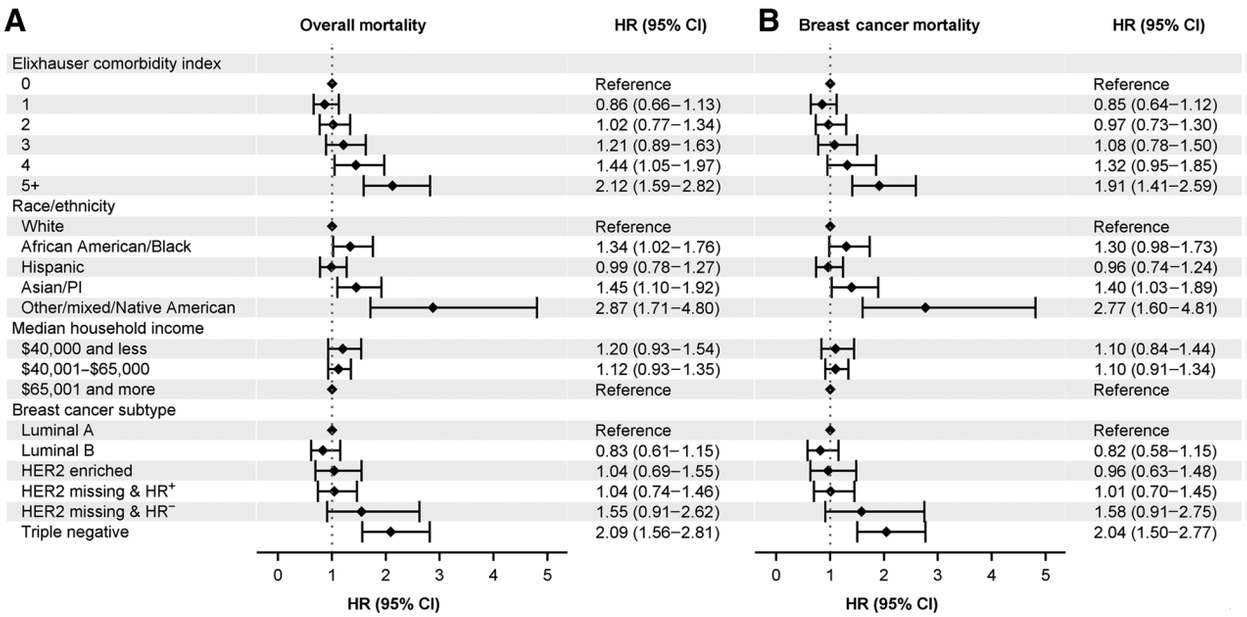

Figure 2.

Adjusted[a] risks of overall mortality (**A,** left) and breast cancer mortality (**B,** right) by selected covariates among women with *de novo* stage IV breast cancer diagnosed 2009–2017, $n = 995$. [a], Models were mutually adjusted by the variables shown in the figure, as well as for age at diagnosis, year of diagnosis, smoking history, median household income, breast cancer subtype, cancer treatments (surgery, palliative chemotherapy, hormonal therapy, immunotherapy, radiotherapy, primary surgery), medical center, and annualized outpatient visit utilization. [b], ECI score *P* value test for trend <0.001.

Comorbidities were common in this cohort, and the prevalence of comorbid diabetes, hypertension, and obesity was greater among African American/Black women. The unadjusted increased risk of overall mortality among African American/Black women was attenuated, but not entirely mitigated after adjustment for comorbidities. In addition, clear patterns of effect modification by comorbidity status on the association of race/ethnicity and all-cause and breast cancer–specific mortality were not seen. The association of race/ethnicity with overall and breast cancer–specific mortality was partially attenuated and consistently lower among those with comorbid conditions or higher ECI scores when stratifying by comorbidities and ECI. Taken together, these results suggest the influence of comorbidities on this association is likely complex and multifactorial. In general, women with comorbidities had a lower mortality risk in our stratified analyses; we hypothesize that clinical management of their comorbidities management might have played a role in their longer survival. Specifically, Latina women had the lowest risks of both breast cancer–specific and overall mortality despite having more risk factors such as diabetes and obesity. Over a third of the cohort had a BMI ≥30 kg/m^2, and obesity was most common among African American/Black and Latina women. Prior studies have found that obesity is strongly correlated with having ≥2 comorbidities, and presenting with higher grade disease and metastases at the time of breast cancer diagnosis (25). Therefore, efforts to ensure that women with metastatic breast cancer receive high-quality care for these comorbidities, in addition to the treatment of their breast cancer, are important and require both coordination and communication among oncology and primary care teams to ensure effective management of these comorbidities. Prior studies suggest team-based cancer care models result in improved quality of life, reduced costs, increased patient satisfaction, and comparable management of symptom burden and psychological effects (26–28). Therefore, improving PCP involvement in cancer care may improve the management of comorbidities among patients with metastatic cancer as well.

Our results also expand upon prior studies which have found racial/ethnic disparities in mortality among women with metastatic breast cancer, without exploring the influence of comorbidities. In our cohort, African American/Black women and Asian/PI women had greater mortality rates despite having health insurance. The presence of insurance alone is not enough to mitigate the disparities in outcomes, as these disparities may also be influenced by differences in breast cancer subtype or tumor biology. In this sample, women with triple-negative disease were more likely to die of breast cancer, even after covariate adjustments. It is also possible that Asian/PI women might have had a higher prevalence of BRCA mutations, but BRCA status is not commonly ascertained as it has not until very recently influenced treatment of an individual woman with metastatic breast cancer (29). Thus, few women in this cohort had BRCA data available.

Prior studies in women with metastatic disease have found strong associations between guideline-concordant therapy, including both the use of endocrine therapy and chemotherapy, and lower mortality rates (30, 31). Although variation in the receipt of these therapies is known to exist by patient race/ethnicity in other healthcare settings (32, 33), we did not find differences in the receipt of palliative therapies or median time to treatment by race/ethnicity in this study. We did however see differences in the receipt of chemotherapy by comorbidity status, with women with greater comorbidities being less likely to receive chemotherapy. It is likely that the mechanisms through which comorbidities influence mortality in women with metastatic breast cancer are multifactorial, and may include differences in treatment receipt, different dose intensities received, and differing complications experienced. It is also possible that those with comorbidities were less likely to get subsequent aggressive cancer therapies that ultimately contributed to their worse prognosis. The presence of

Table 3. Adjusted risks of overall mortality and breast cancer mortality by race/ethnicity, stratified by comorbidity status.

	Event/total	White (non-Hispanic) HR (95% CI)	African American/Black HR (95% CI)	Hispanic HR (95% CI)	Asian/Pacific Islander HR (95% CI)	Other/Mixed/Native American HR (95% CI)
All-cause mortality						
Diabetes						
No	525/830	1.0 (ref)	1.54 (1.14–2.08)	0.99 (0.76–1.30)	1.44 (1.06–1.95)	3.24 (1.87–5.60)
Yes	119/165	1.0 (ref)	1.35 (0.64–2.86)	0.49 (0.24–1.01)	0.99 (0.41–2.37)	0.40 (0.08–2.09)
Hypertension						
No	331/552	1.0 (ref)	2.01 (1.33–3.04)	1.00 (0.73–1.38)	1.38 (0.93–2.05)	2.61 (1.30–5.22)
Yes	313/443	1.0 (ref)	1.24 (0.84–1.82)	0.82 (0.55–1.24)	1.53 (0.99–2.39)	2.54 (1.14–5.68)
Obesity						
No	455/679	1.0 (ref)	1.70 (1.19–2.44)	0.91 (0.67–1.22)	1.45 (1.07–1.98)	2.54 (1.41–4.57)
Yes	189/316	1.0 (ref)	1.32 (0.83–2.11)	1.03 (0.65–1.64)	1.11 (0.50–2.46)	3.01 (0.84–10.83)
Depression						
No	538/840	1.0 (ref)	1.73 (1.30–2.31)	0.97 (0.75–1.26)	1.54 (1.15–2.05)	2.95 (1.73–5.05)
Yes	106/155	1.0 (ref)	1.41 (0.63–3.18)	0.40 (0.18–0.87)	0.52 (0.09–2.91)	1.57 (0.15–16.86)
Elixhauser score (ECI)						
0	143/248	1.0 (ref)	1.92 (0.93–3.96)	0.74 (0.44–1.24)	1.46 (0.79–2.69)	6.70 (2.80–16.06)
1	106/186	1.0 (ref)	1.40 (0.64–3.06)	1.03 (0.54–1.97)	0.62 (0.23–1.67)	3.68 (0.74–18.28)
2	101/172	1.0 (ref)	2.18 (0.77–6.14)	1.56 (0.75–3.24)	2.92 (1.29–6.60)	1.66 (0.24–11.68)
3	75/117	1.0 (ref)	0.53 (0.16–1.79)	0.12 (0.04–0.37)	0.67 (0.18–2.52)	4.23 (0.60–29.75)
4+	219/272	1.0 (ref)	0.90 (0.56–1.47)	0.95 (0.54–1.69)	1.38 (0.76–2.49)	2.53 (0.30–21.16)
Breast cancer–specific mortality						
Diabetes						
No	465/830	1.0 (ref)	1.42 (1.03–1.95)	0.95 (0.72–1.26)	1.35 (0.97–1.88)	3.15 (1.74–5.67)
Yes	103/165	1.0 (ref)	1.74 (0.78–3.90)	0.47 (0.21–1.04)	1.01 (0.40–2.55)	0.39 (0.07–2.11)
Hypertension						
No	293/552	1.0 (ref)	2.10 (1.37–3.21)	0.95 (0.68–1.32)	1.27 (0.82–1.97)	2.64 (1.26–5.54)
Yes	275/443	1.0 (ref)	1.11 (0.73–1.67)	0.85 (0.55–1.32)	1.58 (0.99–2.53)	2.52 (1.07–5.96)
Obesity						
No	397/679	1.0 (ref)	1.63 (1.11–2.39)	0.81 (0.59–1.12)	1.35 (0.96–1.89)	2.31 (1.22–4.39)
Yes	171/316	1.0 (ref)	1.30 (0.79–2.15)	1.10 (0.67–1.78)	1.38 (0.62–3.07)	2.54 (0.69–9.42)
Depression						
No	477/840	1.0 (ref)	1.62 (1.19–2.21)	0.94 (0.71–1.23)	1.47 (1.07–2.00)	2.74 (1.54–4.88)
Yes	91/155	1.0 (ref)	1.26 (0.52–3.06)	0.29 (0.12–0.74)	0.52 (0.08–3.22)	2.09 (0.17–25.03)
Elixhauser score						
0	131/248	1.0 (ref)	1.78 (0.82–3.86)	0.74 (0.43–1.28)	1.60 (0.84–3.06)	6.88 (2.76–17.14)
1	98/186	1.0 (ref)	1.40 (0.61–3.20)	1.03 (0.52–2.04)	0.56 (0.19–1.60)	4.93 (0.96–25.35)
2	91/172	1.0 (ref)	1.21 (0.37–3.96)	1.20 (0.56–2.58)	2.23 (0.94–5.29)	1.28 (0.18–9.13)
3	63/117	1.0 (ref)	0.75 (0.18–3.09)	0.11 (0.03–0.39)	0.76 (0.17–3.37)	7.17 (0.53–97.14)
4+	185/272	1.0 (ref)	0.95 (0.56–1.61)	1.05 (0.57–1.95)	1.39 (0.72–2.67)	2.68 (0.30–23.92)

comorbidities affects clinicians' decision for cancer management and therapeutic options; thus, patients with comorbidities may be less likely than those without comorbidities to receive such treatments (34). In addition, socioeconomic barriers including employment-related concerns, transportation issues, and geographic distance, likely make both access and adherence to systemic treatments more difficult for women, even when insured. In addition, systemic racism, unconscious bias, and/or prior negative experiences with the health care system may also influence the receipt of treatment, although we could not assess these factors in this study. Nevertheless, efforts to address not only barriers related to access but also systemic barriers are needed to ensure that all women receive timely access to guideline-recommended breast cancer treatment (24).

Although this study provides a unique contribution to the evidence about the influence of comorbidities on mortality in women with metastatic breast cancer and utilized a large, diverse cohort of patients in a community-practice setting, some potential limitations warrant comment. First, to decrease heterogeneity, the study sample was limited to women diagnosed with *de novo* metastatic breast cancer and did not include those diagnosed at an earlier stage who later progressed to develop metastatic disease. Therefore, the influence of adherence to initial treatment and to treatments that lower recurrence risk were not assessed in this study. However, this is one of the largest longitudinal studies of metastatic breast cancer from a single community-based healthcare system to date and provides important insight into the influence of comorbidities on mortality outcomes. Second, we defined the presence of comorbidity based on ICD9/10 diagnostic codes, and therefore our conclusions on the influence of comorbidity management, and severity and causality of these conditions on mortality outcomes, as well as the generalizability, may be limited. Additionally, this study did not evaluate biological and lifestyle-related behaviors (besides smoking history and obesity which may be a proxy of physical activity) that may influence the association of comorbidities with mortality. Third, this cohort was followed through 2018, and therefore we cannot make inferences about the influence of expanded targeted and immunotherapies in the metastatic setting in recent years. We also did not analyze breast cancer screening history, which might have varied by race/ethnicity. An interesting

finding was that nearly 30% of the cohort had undergone surgery, which has also been shown in prior studies of women with metastatic breast cancer (35–37). Breast surgeons and medical oncologists might have recommended surgery in certain scenarios to improve quality of life. Such scenarios include large tumors with the threat of growth to skin causing debilitating pain, in limited metastatic disease sites for induction of prolonged remission, addressing the large primary breast mass, or threatened axillary mass causing nerve and functional damage. Despite these limitations, this study provides the necessary foundation for future work in the metastatic setting to elucidate the mechanisms by which comorbidities may be influencing mortality disparities. It also suggests further investigation into whether standard-of-care, guideline-based management for common noncancer comorbidities might influence mortality among metastatic breast cancer patients.

In conclusion, in this diverse, insured population of women with *de novo* metastatic breast cancer, we found medical comorbidities were associated with an increased risk of overall mortality among women, and these comorbidities may influence racial/ethnic disparities in mortality. In addition to ensuring that all women with *de novo* metastatic breast cancer receive guideline-recommended treatment, concurrent clinical management of comorbidities may be important to help reduce mortality.

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Authors' Contributions

L.P. Wallner: Conceptualization, supervision, investigation, visualization, methodology, writing–original draft, writing–review and editing. **L.H. Chen:** Data curation, software, formal analysis, investigation, visualization, methodology, writing–review and editing. **T.A. Hogan:** Conceptualization, writing–original draft, writing–review and editing. **F.M. Brasfield:** Conceptualization, writing–original draft, writing–review and editing. **R. Haque:** Conceptualization, resources, supervision, funding acquisition, investigation, visualization, writing–original draft, project administration, writing–review and editing.

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Note

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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