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Title: The Impact of Functional Limitations on Long-term Outcomes among African-American and White Women with Breast Cancer

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ABSTRACT

Objectives: We examined the impact of functional limitations and functional decline during the first year following breast cancer diagnosis respectively on the risk of mortality from breast cancer and other causes among African-American and white women.

Design: The Health and Functioning in Women (HFW) cohort study.

Setting: Detroit, Michigan, U.S.A.

Participants: A total of 162 African-American and 813 white women aged 40-84 years with newly diagnosed breast cancer identified through the Metropolitan Detroit Cancer Surveillance System (MDCSS) over a 7-month period between 1984 and 1985 and followed for up to 28 years (median follow-up = 11.0 years).

Outcome measures: Risk of mortality from breast cancer and other causes.

Results: Statistically significant increases in the risk of other-cause mortality were found for each unit increase in the number of self-reported functional limitations (HR=1.08, 95% CI 1.03-1.14), 0 versus ≥1 functional limitations (HR=1.47, 95% CI 1.13-1.91), difficulty in pushing or pulling large objects (HR=1.34, 95% CI 1.04-1.73), writing or handling small objects (HR=1.56, 95% CI 1.00-2.44), and walking half a mile (HR=1.60, 95% CI 1.19-2.14). Functional decline was associated with increased risk of other-cause mortality in women with regional and distant disease but not in women with localized disease. Whereas measures of functional limitation were not associated breast cancer-specific mortality, each unit of functional decline (HR=1.34, 95% CI 1.04-1.73) and decline in the ability to sit ≥1 hour (HR=1.17, 95% CI 1.05-1.31) were associated with increased risk of breast cancer-specific mortality. Measures of functional decline

were associated with increased risk of breast-cancer mortality in overweight and obese women, but not in women of normal weight.

Conclusions: Whereas functional limitations were associated with increased risk of other cause mortality, functional decline was associated with increased risk of breast cancer mortality.

ARTICLE SUMMARY

Article Focus:

- The purpose of this study was to assess the long-term prognostic role of functional limitations and functional decline after breast cancer diagnosis in a cohort of African-American and white breast cancer survivors.
- We evaluated whether disparities in the survival of African-American and white women with breast cancer are accounted in part by functional limitations.
- We examined the extent to which the impact of functional limitations on mortality differed as a function of tumor stage and body mass index (BMI).

Key Messages:

- Functional limitations were associated with increased risk of other-cause mortality in this study; functional decline was associated with increased risk of breast cancer-specific mortality.
- Decline in functional status over the first year after breast cancer diagnosis is associated with increased risk of breast cancer-specific mortality.
- Whereas the impact of functional decline on other-cause mortality differs as a function of tumor stage, its impact on breast cancer-specific mortality differs by body mass index (BMI).

Strengths and Limitations:

- This study used comprehensive measures of functional limitations and decline, a prospective population-based cohort design, a relatively large set of white and African-American participants, a long follow-up, and multiple covariates in the tumor-related, lifestyle and socio-demographic domains.

- Functional limitations were self-reported and the majority of respondents were treated with partial or radical mastectomy, which is no longer the standard of care for early stage breast cancer.

Abbreviations and Acronyms:

HFW: Health and Functioning in Women study

BMI: body mass index

HR: hazard ratio

95% CI: 95% confidence interval

MDCSS: Metropolitan Detroit Cancer Surveillance System

kg: kilograms

m^2: meters squared

ICD: International Classification of Diseases

IQ: interquartile range

LACE: Life after Cancer Epidemiology study

INTRODUCTION

Functional limitations at the time of breast cancer diagnosis and following initial treatment have been associated with a number of adverse outcomes among breast cancer survivors [1-4]. Summary measures of physical functioning have been previously evaluated among breast cancer survivors [2 5 6]. Yet the prognostic value of individual limitations versus summary measures of physical functioning and functional decline remains poorly understood. Primary treatment causes functional decline in some breast cancer patients[7-9], and while most recover, some older women do not and may decline even further[10 11]. While functional decline in the first two years after breast cancer diagnosis has been related to 10-year survival among women with breast cancer [12], its impact on longer term survival has not been evaluated. It is also unclear whether any differences in physical functioning exist among population subgroups. For example, older African-American breast cancer patients have been shown to have a disproportionately increased comorbidity burden compared to their white counterparts but it is unknown whether they also have more limitations in physical functioning. A better understanding of the role of functional limitations and decline may provide opportunities to reduce mortality among breast cancer survivors through targeted interventions within high-risk populations[13].

In this study of the long-term prognostic role of functional limitations and functional decline, we considered death from breast cancer and other causes in a cohort of African-American and white breast cancer survivors from the Health and Functioning in Women (HFW) study [5]. A wide age range, the inclusion of both African-American and white women, and a median follow up of 11 years make this cohort particularly suitable for examining racial disparities and the long-term effect of functional limitations and decline while taking into account a wide range of clinical, lifestyle-related, and socio-demographic prognostic factors. We hypothesized that the presence

of functional limitations in the first few months after breast cancer diagnosis and the subsequent decline in functional status over the first year are associated with increased risk of mortality. As disparities in the survival of African-American and white women continue to exist[14 15], we also wished to evaluate whether they could be accounted in part by functional limitations. Obesity is a significant contributor to survival disparities among breast cancer patients [16] and is an important prognostic factor in postmenopausal women[17 18]. Furthermore, although functional limitations have been associated with tumor stage[19], the extent to which disease severity affects the impact of functional limitations on mortality is not well understood[2]. Therefore, we also examined the extent to which the impact of functional limitations on mortality differed as a function of tumor stage and body mass index (BMI).

METHODS

Study Population

The Health and Functioning in Women (HFW) study used in the present analysis has been previously described[5 6]. Briefly, the HFW study was established in 1984 in the Detroit metropolitan area to assess the health, functional, and psychosocial status of women following breast cancer diagnosis. A total of 1,011 eligible participants ages 40-84 with newly diagnosed, histologically confirmed, primary invasive breast cancer identified through the Metropolitan Detroit Cancer Surveillance System (MDCSS) at the Michigan Cancer Foundation, now the Barbara Ann Karmanos Cancer Institute, within 4 weeks of diagnosis and were interviewed in two cohorts. The first cohort consisted of 571 participants ages 55-84, that were identified over a 7-month period between 1984 and 1985; of these, 463 (81.1%) were successfully interviewed between 2 and 4 months following diagnosis. A second cohort of 620 eligible cases, ages 40-54

and 74-84, was identified over a 7-month period between 1987 and 1988; 548 (88.4%) of these participants were successfully interviewed between 2 and 4 months after diagnosis, henceforth referred to as *the baseline interview* or *month 3 interview*. All participants were interviewed a second time approximately 9 months after the first interview, henceforth referred to as *month 12 interview*. The two cohorts were combined and 975 women, for whom complete data were available on all key variables, were included in this analysis.

Functional Limitation Assessment

Respondents were asked at both 3 and 12 month interviews whether they experienced difficulty in performing any of the physical tasks described by Nagi: (i) pushing or pulling large objects, (ii) stooping, crouching, or kneeling, (iii) lifting objects weighing less than 10 pounds, (iv) lifting objects weighting more than 10 pounds, (v) reaching or extending arms above or below shoulder level, (vi) writing or handling small objects, (vii) standing longer than 15 minutes, (viii) sitting longer than an hour, (ix) going up or down a flight of stairs, (x) and walking half a mile [5 6 20]. A woman was considered to have a functional limitation if she reported that the task was completed with a lot of difficulty or avoided on doctor's orders[6]. In this analysis, we considered (a) the effect of individual functional limitations reported at the baseline interview, (b) the effect of the number of functional limitations reported at the 3 month interview as a continuous predictor, and (c) also the effect of a binary predictor indicating the presence of any functional limitation at the 3 month interview (≥1 functional limitations vs. 0) on mortality in order to evaluate a non-linear relationship. We also considered the association of three measures of functional decline between the first and second interviews with mortality. These measures were (1) binary predictors of developing a specific functional limitation between the 3 and 12 month interviews, (2) the number of functional limitations first reported at the month 12 interview as a continuous

predictor, and (3) a binary indicator of any newly reported function limitations (≥1 vs. 0), henceforth referred to as *functional decline*.

Covariates

The covariates used in this analysis were socio-demographic, lifestyle-related, and clinical prognostic factors that, based on the existing literature and *a priori* reasoning, could potentially confound associations between functional limitations and mortality outcomes. Age at diagnosis, breast cancer stage, breast cancer treatment, tumor size, and node involvement were obtained from the MDCSS file, while other variables were obtained from interviews. In analyses, age was used as a continuous variable. Race was coded as either African-American or white. Years of education were recoded into 4 categories: less than high-school, high-school, college, and graduate. The dataset included a binary indicator of financial adequacy (0 for adequate and 1 for inadequate) that was based on self-reported current financial resources and whether they met the participant's needs[6]. BMI was calculated as weight in kilograms/height in meters squared, or kg/m^2, from self-reported weight and height at the baseline interview and used as continuous variable in multivariate models. Smoking status was self-reported and recoded as a binary indicator of whether the participant was a smoker at the time of the interview. A comorbidity index was constructed as the number of previously diagnosed conditions reported by the respondent at the baseline interview from a list of 23 conditions that included diabetes, hypertension, stroke, heart disease, gastrointestinal disease, liver conditions, and primary cancers other than breast cancer, which according to the respondent currently caused some limitation in her activities [6].

Stage of breast cancer at diagnosis was coded as local, regional, or remote. In addition to information on surgery (no surgery, partial mastectomy, or modified radical mastectomy) and

type of adjuvant therapy (radiation or chemotherapy) provided by the MDCSS files, physicians completed a supplementary survey regarding chemotherapy and hormonal therapy administered on an outpatient basis. Data from the two sources were combined to create a two-level treatment variable (no surgery or partial mastectomy, and modified radical mastectomy). The log of the tumor size in millimeters was centered around its mean and used as a continuous variable. The number of positive lymph nodes involved was recoded into a three-level variable (0 nodes, 1-3 nodes, and ≥4 nodes).

Endpoint Ascertainment

Participants were followed until last contact or death as assessed during April 2012, whichever occurred first. Date and cause of death, classified by International Classification of Diseases (ICD) codes version 9, were identified through annual vital status surveillance of all patients in the registry, conducted by MDCSS [21]. ICD codes 174.0-174.9 represented breast cancer deaths and other ICD codes represented death from causes other than breast cancer referred henceforward as other-cause mortality.

Statistical Analysis

Racial differences between continuous variables were assessed using Student t-test and between categorical variables were assessed by Pearson χ^2 or by Fisher's exact test when counts were small. Racial differences in sample medians were assessed using the Wilcoxon Rank Sum test. Kaplan-Meier plots were used to examine the association between functional limitations and mortality. Cox proportional hazards models stratified by age at breast cancer diagnosis with time since diagnosis as the time scale were employed to estimate the association between measures of functional limitation and other-cause and breast cancer mortality [22]. Risk was expressed as a hazard ratio (HR) and 95% confidence interval (CI). The proportionality of hazards assumption

was assessed using Schoenfeld residuals [23]. These tests revealed no significant departures from proportionality. For analyses involving death from breast cancer, participants who died from other causes were removed from the cohort at the time of their death and vice versa. Treatment, tumor stage, tumor size, node involvement, race, BMI, financial adequacy, education, smoking status, and period of entry were considered as potential confounders in all multivariate analyses. To evaluate effect modification we conducted analyses separately for subgroups defined by BMI (<25, 25-30, >30) at the baseline interview and stage of breast cancer (local, remote or distant) at diagnosis. We combined women in the distant and remote categories due to the small number of respondents with distant disease (n=55). The type I error was set at .05 and all reported *P*-values are two-sided. Analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC) and R version 2.15.

RESULTS

The demographic and clinical characteristics of African-American (n=162; 16.6%) and white women (n=813; 83.3%) with breast cancer are presented in **Table 1**. Overall, the median follow-up time was 11.0 years (interquartile range [IQ]: 4.5-22.4 years). Median follow-up was significantly shorter for African-American women than their white counterparts (median =9.0 years [IQ: 3.0-19.0] vs. 12.0 [IQ: 4.8-22.7] years, P=0.0003). Among those who survived, African-American women (n=28) and white women (n=193) had similar follow-up (median =24.3 years vs. 24.4 years, P=0.07), which suggests that the difference in median survival between African-American and white women is due to increased mortality among African-American women. During this period, there were 753 deaths; 317 were due breast cancer and 436 were due to other causes. Slightly more African-American women died of breast cancer than

white women (37.7% vs. 31.5%, P=0.13). There were no racial differences in the proportion of other-cause deaths (44.4% vs. 44.8%, P=0.94). The distribution of age was also similar in both groups. Compared to white women, African-American women had significantly fewer years of education (24.7% vs. 28.3% respectively had ≥12 years of education, P<0.0001), greater mean BMI (28.2 kg/m^2 vs. 25.9 kg/m^2, P<0.0001), and fewer reported adequate financial resources (66.7% vs. 86.0% respectively, P<0.0001). African-American women were less likely than their white counterparts to have localized disease (43.8% vs. 55.6% respectively, P=0.01) at the time of breast cancer diagnosis. Additionally, African-American women were more likely to have regional disease (48.1% vs. 39.2% respectively, P=0.04), receive no surgery (3.7% vs. 1.4% respectively, P=0.04), and have larger tumors, with mean tumor sizes of 38.2 (SD=26.2) and 32.8 (SD=24.7) millimeters for African-American and white women respectively (P=0.01).

The distributions of summary measures of functional limitations overall and by race are presented in **Table 1** and distributions of specific functional limitations are presented in **Figures 1a** and **1b.** At three months after breast cancer diagnosis, African-American women were more likely to report any functional limitations (83.3% vs. 67.3%, P<0.0001) and a greater number of functional limitations than their white counterparts (mean 2.8 [SD=2.3] and 2.1 [SD=2.3], P=0.0003). African-Americans were more likely than whites to report difficulty in pushing or pulling large objects (66.1% vs. 48.0%, P<0.0001), lifting less 10 pounds (33.3% vs. 19.3%, P<0.0001), lifting more than 10 pounds (62.4% vs. 42.9%, P<0.0001), going up or down a flight of stairs (17.3% vs. 11.7%, P=0.05), and walking half a mile (29.6% vs. 22.1%, P=0.04). In addition to having a greater mean increase in the number of functional limitations during the first year after diagnosis (0.6 [SD=1.4] vs. 0.4 [SD=0.9], P=0.03), a larger proportion of African-

American women reported difficulty going up or down a flight of stairs at month 12 but not month 3 (16.7% vs. 9.0%, P=0.003).

Other-cause mortality

Comparing white women with versus without functional limitations, Kaplan-Meier plots show considerably shorter other-cause survival for those with functional limitations (**Figure 2a**). Overall, African-American women with or without functional limitations have shorter survival than their white counterparts. However, the survival curve of African-American women with functional limitations is not considerably different than that of their white counterparts. Difficulties in pushing or pulling large objects (HR=1.34, 95% CI 1.04-1.73), writing or handling small objects (HR=1.56, 95% CI 1.00-2.44), walking half a mile (HR=1.60, 95% CI 1.19-2.14), each unit increase in the number of self-reported functional limitations (HR=1.08, 95% CI 1.03-1.14), as well as experiencing any functional limitation (HR=1.47, 95% CI 1.13-1.91) were all associated with statistically significant increases in the risk of other-cause mortality (**Table 2**). Functional decline was not associated with other-cause mortality. When evaluating effect modification by stage, we found that the number of functional limitations (HR=1.11, 95% CI 1.03-1.19) as well as 0 vs. ≥1 functional limitations (HR=1.46, 95% CI 1.05-2.03) were significantly associated with other-cause mortality in women with localized disease but not in those with regional or distant disease, whereas functional decline was associated with increased risk of other-cause mortality in women with regional and distant disease (HR=1.61, 95% CI 1.03-2.52), but not in those with localized disease.

Breast cancer-specific mortality

Kaplan-Meier plots of breast cancer survival indicate that African-American women had poorer survival than white women (**Figure 2b**). Furthermore, within racial groups women with functional limitations had slightly poorer survival than those without limitations. In multivariate models, we found no evidence of an association between any of the measures of functional limitations and breast cancer-specific mortality in this group (**Table 2**). On the other hand, each unit of functional decline (HR=1.34, 95% CI 1.04-1.73) and decline in the ability to sit ≥1 hour (HR=1.17, 95% CI 1.05-1.31) were both significantly associated with increased risk of breast cancer mortality. Each unit increase in the number of functional limitations was positively associated with other-cause mortality in overweight (BMI 25-30; HR=1.17, 95% CI 1.05-1.31) and obese women (BMI>30; HR=1.48, 95% CI 1.09-2.02), but not in women of normal weight (BMI<25; HR=1.13, 95% CI 0.94-1.36). Functional decline was positively associated with breast cancer mortality in obese women (HR=3.05, 95% CI 1.32-7.03).

DISCUSSION

We found that the presence of functional limitations after breast cancer diagnosis, including difficulties in mobility (walking half a mile) and in upper-body limitations (pushing or pulling large objects, writing or handling small objects) were associated with statistically significant increases in the risk of other-cause mortality compared to those with breast cancer without such limitations in this biracial cohort. The presence of functional limitations was statistically significantly associated with other-cause mortality in women with localized disease, but not in women with regional and distance disease. Conversely, functional decline was associated with increased risk of other-cause mortality in women with regional and distant disease, but not in women with localized disease. Each unit of functional decline and decline in lower-body

function (the ability to sit for an hour or longer) were both significantly associated with increased risk of breast cancer mortality. Analyses stratified by BMI revealed that the number of functional limitations was positively associated with other-cause mortality in overweight and obese women, but not in women of normal weight. Functional decline was positively associated with breast cancer mortality in obese women.

This study extends earlier work that reported on diminished quality of life and self-reported functional limitations as predictors of decreased overall and non-breast cancer survival [2 24] to show that limitations in lower body function and any functional decline during the first year after breast cancer diagnosis are strong predictors of breast cancer mortality. We found that functional decline has prognostic value for breast cancer independently of other prognostic factors and comorbidity; the impact of functional decline during the first year following breast cancer diagnosis is stronger in women with regional and remote disease. To our knowledge, this is the first study to evaluate the association of both individual limitations and functional decline with survival among breast cancer patients. Our findings underscore the predictive value of comprehensive measures of functional limitations.

Biological mechanisms by which functional limitations affect survival of breast cancer patients are not well understood. Chronic inflammation has been between linked to diminished physical functioning and disability in populations of older adults [25-30] and may underlie the observed association of functional limitations with mortality. Functional limitations and cancer may synergistically increase inflammation resulting in disease progression and mortality.

In addition to our inability to address the underlying biological mechanisms, another important limitation of this study is that the majority of respondents were treated with partial or radical

mastectomy, which is no longer the standard of care for early stage breast cancer. The currently recommended standard of care for this population consisting of radiation and segmental mastectomy or lumpectomy may have less impact on function. Modern surgical techniques may also reduce the functional impact of breast cancer surgery. Furthermore, the observed patterns of functional limitations in this study may have been affected by the fact that a relatively small number of participants received adjuvant chemotherapy or hormone therapy. Although the self-reported nature of functional limitations in this study may be subject to bias, self-reported functional limitations have been shown to correlate with performance-based measures[10]. Another limitation of the current study is our inability to compare whether women with breast cancer have a similar burden of functional limitations as women without breast cancer, and whether the impact of functional limitations on other-cause mortality differs in women with and without breast cancer.

The strengths of the study include comprehensive measures of functional limitations and decline, a prospective population-based cohort design, a relatively large set of white and African-American participants, a long follow-up, and our ability to take into account multiple covariates in the tumor-related, lifestyle and socio-demographic domains. Since women in this study were identified through a large regional population-based surveillance program, our findings may apply to wider audiences than studies in which subjects were drawn from academic settings. Bias due to loss of follow-up was minimized because mortality status was ascertained annually for all the patients in the registry.

In summary, our findings indicate that functional limitations and functional decline during the first year following breast cancer diagnosis are associated with the breast cancer-specific and other-cause mortality of women with breast cancer.

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Tables and legends for figures

Table 1: Characteristics of the study group overall and by race

	Overall N = 975	African-American N = 162	White N = 813	P value
Age at diagnosis, mean ± SD	63 ± 12.4	62.5 ± 12.6	63.1 ± 12.4	0.59
Follow-up (years), Median (Q1, Q3)	11 (4.5,22.4)	9 (3,19)	12 (4.8,22.7)	0.0003
Financial adequacy	807 (82.8)	108 (66.7)	699 (86)	<.0001
Highest level of educational attainment, *N (%)*				
Less than high-school	375 (38.5)	89 (54.9)	286 (35.2)	<.0001
High-school	330 (33.8)	33 (20.4)	297 (36.5)	
College	210 (21.5)	32 (19.8)	178 (21.9)	
Graduate	60 (6.2)	8 (4.9)	52 (6.4)	
Body mass index (kg/m^2), mean ± SD	26.3 ± 5.3	28.2 ± 5.4	25.9 ± 5.1	<.0001
Stage, N *(%)*				
Local	523 (53.6)	71 (43.8)	452 (55.6)	0.01
Regional	397 (40.7)	78 (48.1)	319 (39.2)	0.04
Remote	55 (5.6)	13 (8)	42 (5.2)	0.15
Smoking, N *(%) current smokers*	195 (20)	37 (22.8)	158 (19.4)	0.32
Breast cancer treatment, N *(%)*				
No surgery	17 (1.7)	6 (3.7)	11 (1.4)	0.04
Partial mastectomy	194 (19.9)	29 (17.9)	165 (20.3)	0.49
Modified radical mastectomy	760 (77.9)	126 (77.8)	634 (78)	0.95
Number of lymph nodes involved, N *(%)*				
0	443 (45.4)	60 (37)	383 (47.1)	0.10
1-3	302 (31)	57 (35.2)	245 (30.1)	
≥4	39 (4)	10 (6.2)	29 (3.6)	
Tumor Size (mm), mean ± SD	33.7 ± 25	38.2 ± 26.2	32.8 ± 24.7	0.01
Comorbidity index, mean ± SD	2.2 ± 1.5	2.2 ± 1.6	2.2 ± 1.5	0.91
Functional limitations at 3 months after breast cancer diagnosis				
No. functional limitations, mean ± SD	2.2 ± 2.3	2.8 ± 2.3	2.1 ± 2.3	0.0003
≥1 functional limitation, N (%)	682 (69.9)	135 (83.3)	547 (67.3)	<.0001
Functional decline between baseline and 12 months				
No. functional limitation at month 12 and not 3, mean ± SD	0.4 ± 1	0.6 ± 1.4	0.4 ± 0.9	0.03
≥1 additional functional limitation reported at month 12, N (%)	212 (21.7)	36 (22.2)	176 (21.6)	0.87

Mortality, *N (%)*				
All-cause	753 (77.3)	133 (82.6)	620 (76.3)	0.08
Breast cancer-specific	317 (32.5)	61 (37.7)	256 (31.5)	0.13
Other-cause	436 (44.7)	72 (44.4)	364 (44.8)	0.94

Table 2: Hazard ratios (and 95% confidence intervals) of functional limitations for mortality *

Covariate	Other Cause Mortality (No. deaths = 436)		Breast Cancer Mortality (No. deaths = 317)	
	Baseline	**Decline**	**Baseline**	**Decline**
Model 1				
African-American	1.23 (0.91, 1.66)	1.19 (0.88, 1.62)	1.04 (0.76, 1.44)	1.08 (0.78, 1.49)
Model 2				
African-American	1.19 (0.87, 1.62)	1.19 (0.88, 1.62)	1.12 (0.81, 1.55)	1.08 (0.78, 1.49)
Difficulty pushing/pulling large objects (yes/no)	1.34 (1.04, 1.73)	0.98 (0.67, 1.43)	0.77 (0.58, 1.03)	1.41 (0.93, 2.13)
Difficulty stooping/crouching/kneeling (yes/no)	1.02 (0.77, 1.35)	0.97 (0.65, 1.45)	1.39 (0.99, 1.94)	0.94 (0.56, 1.57)
Difficulty lifting less than 10 pounds (yes/no)	0.92 (0.68, 1.25)	0.91 (0.53, 1.56)	1.05 (0.72, 1.53)	1.27 (0.65, 2.48)
Difficulty lifting ≥10 pounds (yes/no)	0.99 (0.75, 1.30)	1.07 (0.71, 1.60)	0.78 (0.56, 1.07)	1.20 (0.76, 1.89)
Difficulty extending arm above shoulder level (yes/no)	0.97 (0.72, 1.31)	0.94 (0.56, 1.58)	0.85 (0.58, 1.23)	0.92 (0.49, 1.76)
Difficulty writing/handling small objects (yes/no)	1.56 (1.00, 2.44)	0.47 (0.22, 1.03)	1.61 (0.95, 2.73)	1.19 (0.53, 2.68)
Difficulty standing more than 15 minutes (yes/no)	0.81 (0.58, 1.13)	1.33 (0.87, 2.02)	0.91 (0.62, 1.35)	1.58 (0.96, 2.62)
Difficulty sitting more than an hour (yes/no)	0.77 (0.49, 1.22)	1.75 (0.99, 3.09)	1.04 (0.63, 1.73)	2.06 (1.13, 3.76)
Difficulty going up/down a flight of stairs (yes/no)	1.29 (0.93, 1.78)	1.18 (0.82, 1.69)	1.07 (0.70, 1.63)	0.61 (0.37, 1.01)
Difficulty walking half a mile (yes/ no)	1.60 (1.19, 2.14)	1.34 (0.90, 2.00)	1.24 (0.88, 1.77)	1.32 (0.82, 2.13)
Model 3				
African-American	1.22 (0.90, 1.65)	1.19 (0.88, 1.61)	1.05 (0.76, 1.44)	1.01 (0.73, 1.40)
Functional limitations (continuous)	1.08 (1.03, 1.14)	1.10 (1.00, 1.21)	0.99 (0.93, 1.05)	1.17 (1.05, 1.31)
Model 4				
African-American	1.17 (0.87, 1.59)	1.21 (0.90, 1.63)	1.08 (0.78, 1.50)	1.04 (0.75, 1.43)
Functional limitations (≥1 vs. 0)	1.47 (1.13, 1.91)	1.17 (0.92, 1.50)	0.75 (0.56, 0.98)	1.26 (0.94, 1.69)

*Models were stratified by age at breast cancer diagnosis and additionally adjusted for stage of breast cancer, treatment, body mass index, financial adequacy, education, smoking, positive lymph node involvement, tumor size at diagnosis, and period of study entry.

Table 3: Hazard ratios (and 95% confidence intervals) of functional limitations for mortality stratified by tumor stage and body mass index*

	Other Cause Mortality (No. deaths = 436)		Breast Cancer Mortality (No. deaths = 317)	
	Baseline	**Decline**	**Baseline**	**Decline**
Stage of breast cancer at diagnosis*				
Local, N=523	*No. of deaths = 274*		*No. of deaths = 93*	
Functional limitations (continuous)	1.11 (1.03, 1.19)	1.07 (0.94, 1.23)	1.04 (0.92, 1.17)	1.16 (0.97, 1.38)
Functional limitations (≥1 vs. 0)	1.46 (1.05, 2.03)	1.06 (0.75, 1.49)	1.30 (0.76, 2.23)	1.02 (0.59, 1.77)
Regional and Distant, N=452	*No. of deaths = 162*		*No. of deaths = 224*	
Functional limitations (continuous)	1.03 (0.94, 1.14)	1.19 (1.00, 1.43)	1.02 (0.94, 1.10)	1.08 (0.92, 1.26)
Functional limitations (≥1 vs. 0)	1.58 (0.90, 2.75)	1.61 (1.03, 2.52)	0.66 (0.47, 0.93)	1.19 (0.82, 1.73)
Body mass index at baseline, (kg/m^2)†				
<25, N=454	*No. of deaths = 210*		*No. of deaths = 128*	
Functional limitations (continuous)	1.11 (1.01, 1.22)	1.12 (0.94, 1.32)	1.01 (0.90, 1.14)	1.13 (0.94, 1.36)
Functional limitations (≥1 vs. 0)	1.80 (1.14, 2.84)	1.45 (0.93, 2.27)	0.74 (0.46, 1.18)	1.00 (0.57, 1.73)
25-30, N=323	*No. of deaths = 148*		*No. of deaths = 109*	
Functional limitations (continuous)	1.07 (1.02, 1.13)	1.10 (1.00, 1.21)	0.99 (0.93, 1.06)	1.17 (1.05, 1.31)
Functional limitations (≥1 vs. 0)	1.48 (1.13, 1.94)	1.24 (0.95, 1.60)	0.71 (0.54, 0.95)	1.28 (0.94, 1.73)
>30, N=198	*No. of deaths = 78*		*No. of deaths = 80*	
Functional limitations (continuous)	0.78 (0.60, 1.02)	1.09 (0.68, 1.76)	1.08 (0.92, 1.27)	1.48 (1.09, 2.02)
Functional limitations (≥1 vs. 0)	0.62 (0.18, 2.12)	2.15 (0.70, 6.60)	1.50 (0.61, 3.66)	3.05 (1.32, 7.03)

*Models were stratified by age at breast cancer diagnosis and additionally adjusted for breast cancer treatment, body mass index, financial adequacy, education, smoking, positive lymph node involvement, tumor size at diagnosis, and period of study entry.

†Models were stratified by age at breast cancer diagnosis and additionally adjusted for breast cancer stage, treatment, financial adequacy, education, smoking, positive lymph node involvement, tumor size at diagnosis, and period of study entry.

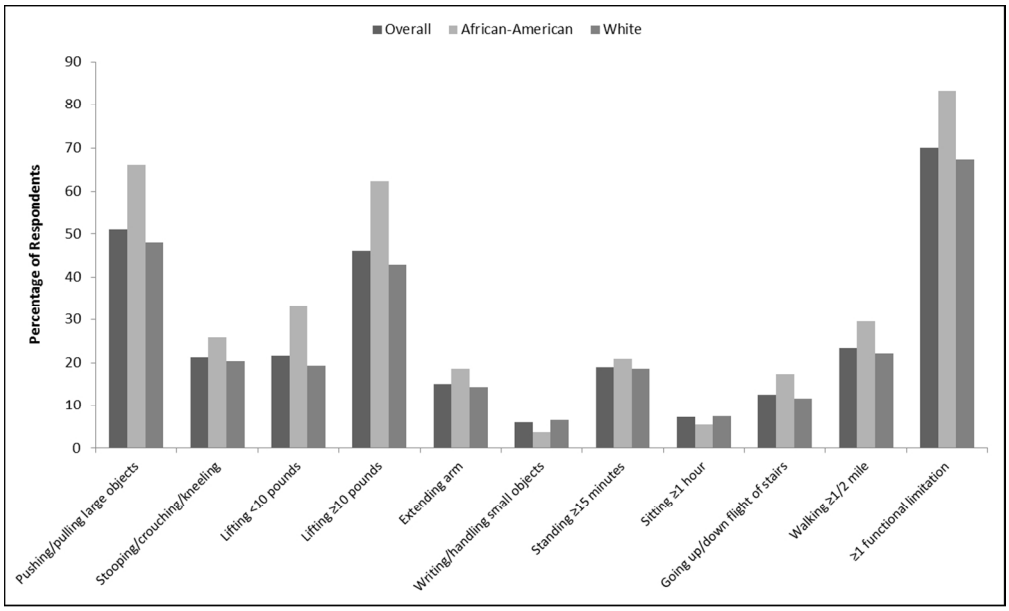

Figure 1a: Distribution of functional limitations reported at 3 months following breast cancer diagnosis

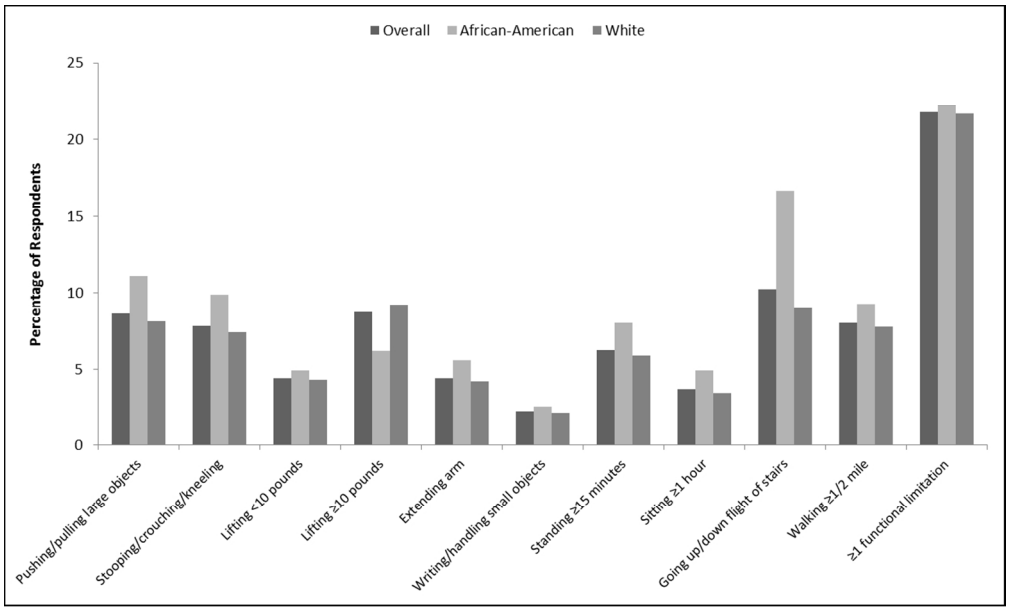

Figure 1b: Distribution of functional decline between the 3 and 12 months following breast cancer diagnosis

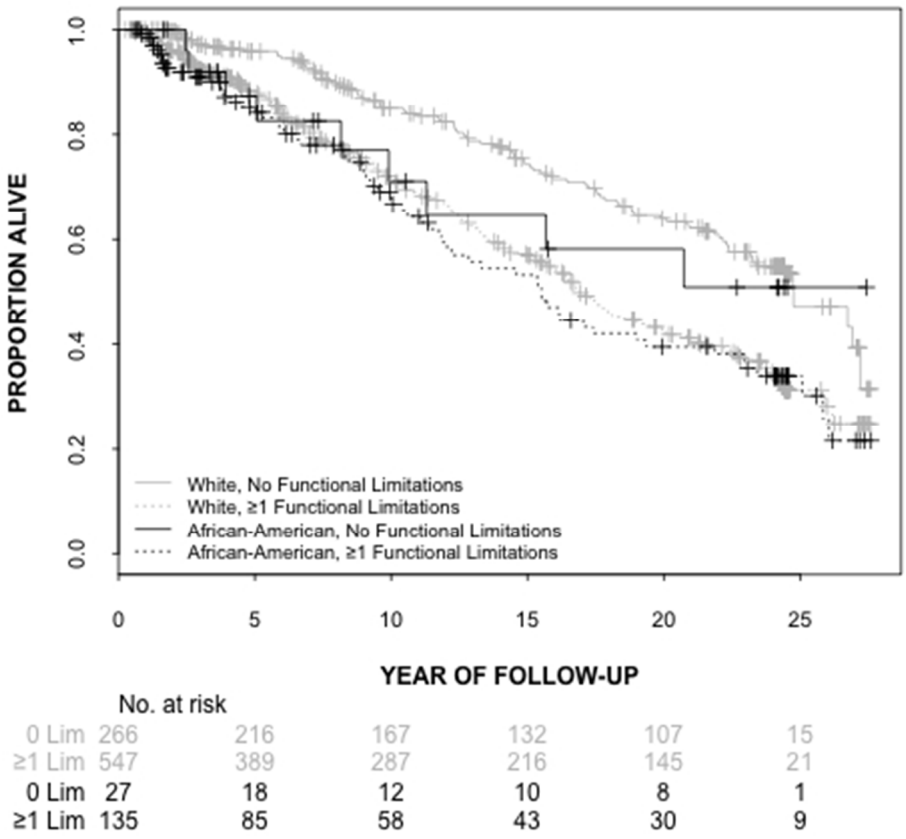

Figure 2a: Kaplan-Meier estimates of other-cause survival by race and category of functional limitations (0 vs. ≥ 1)
169x169mm (72 x 72 DPI)

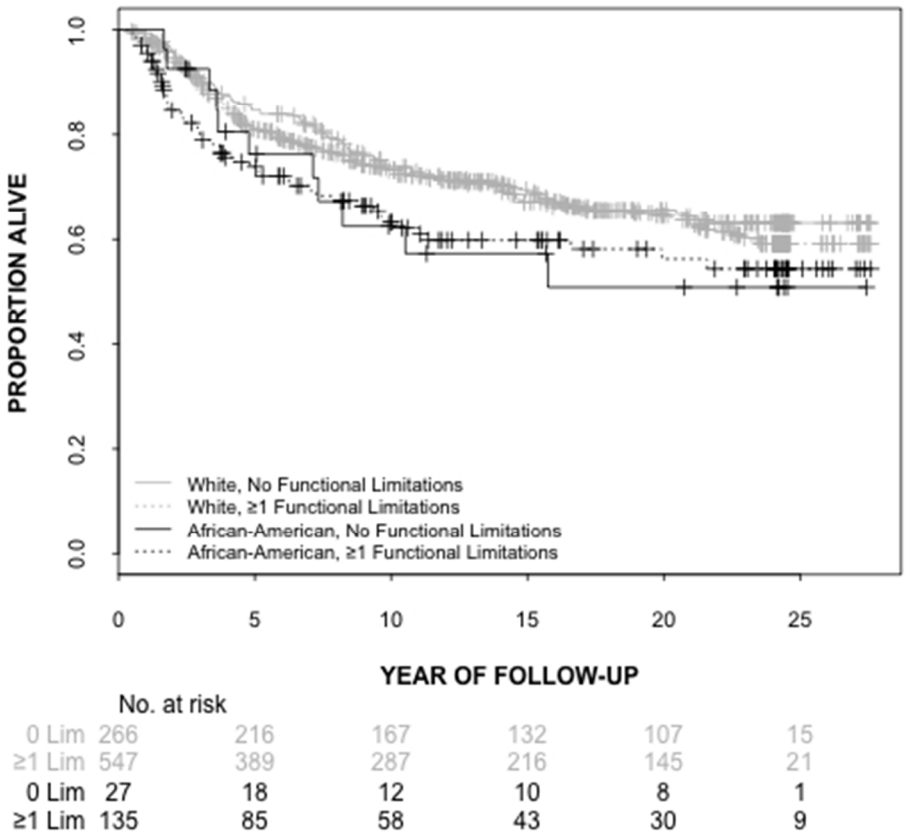

Figure 2b: Kaplan-Meier estimates of breast cancer survival by race and category of functional limitations (0 vs. ≥ 1)
169x169mm (72 x 72 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **A description of the study design is included in the abstract.**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **The abstract summarizes findings, and implications**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **We explain the scientific background and rationale in page 5 of the main document.**
Objectives	3	State specific objectives, including any pre-specified hypotheses **Have stated our hypothesis in pages 5, 6.**
Methods		
Study design	4	Present key elements of study design early in the paper **Elements of study design are presented in the "Study Population" section of methods.**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **This information is presented in the "Study Population" section of methods**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Eligibility criteria is also presented in the "Study Population" section.**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **Does not apply to our study.**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Exposures are described in the section "Functional limitations". Outcome is described in section "Endpoint Ascertainment". Potential confounders are listed under the heading "Covariates".**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **We have done so throughout the "Methods" section.**
Bias	9	Describe any efforts to address potential sources of bias. **Discussed in methods.**
Study size	10	Explain how the study size was arrived at **Exclusion criteria are described in the "Methods" section.**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **A detailed description of statistical methods is provided in the manuscript.**
		(*b*) Describe any methods used to examine subgroups and interactions **Effect modification was evaluated by analysing subgroups separately. A detailed description is provided in the "Methods" section.**
		(*c*) Explain how missing data were addressed **No data were missing.**
		(*d*) If applicable, explain how loss to follow-up was addressed

		A description is provided in the "Methods" section.
		(*e*) Describe any sensitivity analyses **None were conducted.**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed**:** **This information is provided in the "Study Population" section.**
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Table 1 presents this data.**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount) **Summarized in Table 1**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Reported in Tables 2 and 3**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Legends are provided for Tables 2 and 3 along with a listing of the confounders.**
		(*b*) Report category boundaries when continuous variables were categorized **Explained categories used in methods.**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Table 3presents findings for subgroup analyses.**
Discussion		
Key results	18	Summarise key results with reference to study objectives **We summarise key findings in the first paragraph of the discussion section.**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **We list a number of limitations in the discussion section.**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results **We provide a discussion of generalisability.**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Sources of funding and the role of funders are listed in the main document.**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

The Impact of Functional Limitations on Long-term Outcomes among African-American and White Women with Breast Cancer: A Cohort Study

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Title: The Impact of Functional Limitations on Long-term Outcomes among African-American and White Women with Breast Cancer**: A Cohort Study**

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Text Word Count: 3152; Abstract Word Count: 309; Tables: 3; Figures: 2; References: 30

ABSTRACT

Objectives: We examined the impact of functional limitations and functional decline during the first year following breast cancer diagnosis respectively on the risk of mortality from breast cancer and other causes among African-American and white women.

Design: The Health and Functioning in Women cohort study.

Setting: Detroit, Michigan, U.S.A.

Participants: A total of 162 African-American and 813 white women aged 40-84 years with newly diagnosed breast cancer identified through the Metropolitan Detroit Cancer Surveillance System over a 7-month period between 1984 and 1985 and followed for up to 28 years (median 11.0 years).

Outcome measures: Risk of mortality from breast cancer and other causes.

Results: Statistically significant increases in the risk of other-cause mortality were found for each unit increase in the number of self-reported functional limitations (HR=1.08, 95% CI 1.03-1.14), 0 versus ≥1 functional limitations (HR=1.47, 95% CI 1.13-1.91), difficulty in pushing or pulling large objects (HR=1.34, 95% CI 1.04-1.73), writing or handling small objects (HR=1.56, 95% CI 1.00-2.44), and walking half a mile (HR=1.60, 95% CI 1.19-2.14). Functional limitations and decline did not explain racial disparities in the survival of this cohort. Functional decline was associated with increased risk of other-cause mortality in women with regional and remote disease but not in women with localized disease. Whereas measures of functional limitation were not associated with breast cancer-specific mortality, each unit of functional decline (HR=1.17, 95% CI 1.05-1.31) and decline in the ability to sit ≥1 hour (HR=2.06, 95% CI 1.13-3.76) were associated with increased risk of breast cancer-specific mortality. Measures of

functional decline were associated with increased risk of breast-cancer mortality in overweight and obese women, but not in women of normal weight.

Conclusions: Whereas functional limitations were associated with increased risk of other cause mortality, functional decline was associated with increased risk of breast cancer mortality.

ARTICLE SUMMARY

Article Focus:

- The purpose of this study was to assess the long-term prognostic role of functional limitations and functional decline after breast cancer diagnosis in a cohort of African-American and white breast cancer survivors.
- We evaluated whether disparities in the survival of African-American and white women with breast cancer are accounted in part by functional limitations.
- We examined the extent to which the impact of functional limitations on mortality differed as a function of tumor stage and body mass index (BMI).

Key Messages:

- Functional limitations were associated with increased risk of other-cause mortality in this study; functional decline was associated with increased risk of breast cancer-specific mortality.
- Decline in functional status over the first year after breast cancer diagnosis is associated with increased risk of breast cancer-specific mortality.
- Whereas the impact of functional decline on other-cause mortality differs as a function of tumor stage, its impact on breast cancer-specific mortality differs by body mass index (BMI).
- Functional limitations did not explain survival disparities among African-American and white women with breast cancer.

Strengths and Limitations:

- This study used comprehensive measures of functional limitations and decline, a prospective population-based cohort design, a relatively large set of white and African-

American participants, a long follow-up, and multiple covariates in the tumor-related, lifestyle and socio-demographic domains.

- Functional limitations were self-reported and the majority of respondents were treated with partial or radical mastectomy, which is no longer the standard of care for early stage breast cancer.

Abbreviations and Acronyms:

HFW: Health and Functioning in Women study

BMI: body mass index

HR: hazard ratio

95% CI: 95% confidence interval

MDCSS: Metropolitan Detroit Cancer Surveillance System

kg: kilograms

m^2: meters squared

ICD: International Classification of Diseases

IQ: interquartile range

LACE: Life after Cancer Epidemiology study

INTRODUCTION

Functional limitations at the time of breast cancer diagnosis and following initial treatment have been associated with a number of adverse outcomes among breast cancer survivors [1-4]. Summary measures of physical functioning have been previously evaluated among breast cancer survivors [2 5 6]. Yet the prognostic value of individual limitations versus summary measures of physical functioning and functional decline remains poorly understood. Primary treatment causes functional decline in some breast cancer patients[7-9], and while most recover, some older women do not and may decline even further[10 11]. While functional decline in the first two years after breast cancer diagnosis has been related to 10-year survival among women with breast cancer [12], its impact on longer term survival has not been evaluated. It is also unclear whether any differences in physical functioning exist among population subgroups. For example, older African-American breast cancer patients have been shown to have a disproportionately increased comorbidity burden compared to their white counterparts but it is unknown whether they also have more limitations in physical functioning. A better understanding of the role of functional limitations and decline may provide opportunities to reduce mortality among breast cancer survivors through targeted interventions within high-risk populations[13].

In this study of the long-term prognostic role of functional limitations and functional decline, we considered death from breast cancer and other causes in a cohort of African-American and white breast cancer survivors from the Health and Functioning in Women (HFW) study [5]. A wide age range, the inclusion of both African-American and white women, and a median follow up of 11 years make this cohort particularly suitable for examining racial disparities and the long-term effect of functional limitations and decline while taking into account a wide range of clinical, lifestyle-related, and socio-demographic prognostic factors. We hypothesized that the presence

of functional limitations in the first few months after breast cancer diagnosis and the subsequent decline in functional status over the first year are associated with increased risk of mortality. As disparities in the survival of African-American and white women continue to exist[14 15], we also wished to evaluate whether they could be accounted in part by functional limitations. Obesity is a significant contributor to survival disparities among breast cancer patients [16] and is an important prognostic factor in postmenopausal women[17 18]. Furthermore, although functional limitations have been associated with tumor stage[19], the extent to which disease severity affects the impact of functional limitations on mortality is not well understood[2]. Therefore, we also examined the extent to which the impact of functional limitations on mortality differed as a function of tumor stage and body mass index (BMI).

METHODS

Study Population

The Health and Functioning in Women (HFW) study used in the present analysis has been previously described[5 6]. Briefly, the HFW study was established in 1984 in the Detroit metropolitan area to assess the health, functional, and psychosocial status of women following breast cancer diagnosis. A total of 1,011 eligible participants ages 40-84 with newly diagnosed, histologically confirmed, primary invasive breast cancer identified through the Metropolitan Detroit Cancer Surveillance System (MDCSS) at the Michigan Cancer Foundation, now the Barbara Ann Karmanos Cancer Institute, within 4 weeks of diagnosis and were interviewed in two cohorts. The first cohort consisted of 571 participants ages 55-84, that were identified over a 7-month period between 1984 and 1985; of these, 463 (81.1%) were successfully interviewed between 2 and 4 months following diagnosis. A second cohort of 620 eligible cases, ages 40-54

and 74-84, was identified over a 7-month period between 1987 and 1988; 548 (88.4%) of these participants were successfully interviewed between 2 and 4 months after diagnosis, henceforth referred to as *the baseline interview* or *month 3 interview*. All participants were interviewed a second time approximately 9 months after the first interview, henceforth referred to as *month 12 interview*. The two cohorts were combined and 975 women, for whom complete data were available on all key variables, were included in this analysis. This study was approved by the Committee on Human Research at the University of California, San Francisco. Additionally, the HFW study was approved at the time of its inception by the Human Subjects Committee at the Michigan Cancer Foundation.

Functional Limitation Assessment

Respondents were asked at both 3 and 12 month interviews whether they experienced difficulty in performing any of the physical tasks described by Nagi: (i) pushing or pulling large objects, (ii) stooping, crouching, or kneeling, (iii) lifting objects weighing less than 10 pounds, (iv) lifting objects weighting more than 10 pounds, (v) reaching or extending arms above or below shoulder level, (vi) writing or handling small objects, (vii) standing longer than 15 minutes, (viii) sitting longer than an hour, (ix) going up or down a flight of stairs, (x) and walking half a mile [5 6 20]. A woman was considered to have a functional limitation if she reported that the task was completed with a lot of difficulty or avoided on doctor's orders[6]. In this analysis, we considered (a) the effect of individual functional limitations reported at the baseline interview, (b) the effect of the number of functional limitations reported at the 3 month interview as a continuous predictor, and (c) also the effect of a binary predictor indicating the presence of any functional limitation at the 3 month interview (≥1 functional limitations vs. 0) on mortality in order to evaluate a non-linear relationship. We also separately considered the association of three measures of functional

decline between the first and second interviews with mortality. These measures were (1) binary predictors of developing a specific functional limitation between the 3 and 12 month interviews, (2) the number of functional limitations first reported at the month 12 interview as a continuous predictor, and (3) a binary indicator of any newly reported function limitations (≥1 vs. 0), henceforth referred to as *functional decline*.

Covariates

The covariates used in this analysis were socio-demographic, lifestyle-related, and clinical prognostic factors that, based on the existing literature and *a priori* reasoning, could potentially confound associations between functional limitations and mortality outcomes. Age at diagnosis, breast cancer stage, breast cancer treatment, tumor size, and node involvement were obtained from the MDCSS file, while other variables were obtained from interviews. In analyses, age was used as a continuous variable. Race was coded as either African-American or white. Years of education were recoded into 4 categories: less than high-school, high-school, college, and graduate. The dataset included a binary indicator of financial adequacy (0 for adequate and 1 for inadequate) that was based on self-reported current financial resources and whether they met the participant's needs[6]. BMI was calculated as weight in kilograms/height in meters squared, or kg/m^2, from self-reported weight and height at the baseline interview and used as continuous variable in multivariate models. Smoking status was self-reported and recoded as a binary indicator of whether the participant was a smoker at the time of the interview. A comorbidity index was constructed as the number of previously diagnosed conditions reported by the respondent at the baseline interview from a list of 23 conditions that included diabetes, hypertension, stroke, heart disease, gastrointestinal disease, liver conditions, and primary cancers

other than breast cancer, which according to the respondent currently caused some limitation in her activities [6].

Stage of breast cancer at diagnosis was coded as local, regional, or remote. In addition to information on surgery (no surgery, partial mastectomy, or modified radical mastectomy) provided by the MDCSS files, physicians completed a supplementary survey regarding chemotherapy and hormonal therapy administered on an outpatient basis. However, adjuvant therapy utilization has been shown to be underreported in SEER registries[21], resulting in a small number of participants with evidence of chemotherapy and/or hormonal therapy treatment in addition to partial or radical mastectomy. Less than 30 women received no surgery. We combined data from the MDCSS files and physician surveys to create a two-level treatment variable (no surgery or partial mastectomy, and modified radical mastectomy). The log of the tumor size in millimeters was centered around its mean and used as a continuous variable. The number of positive lymph nodes involved was recoded into a three-level variable (0 nodes, 1-3 nodes, and ≥4 nodes).

Endpoint Ascertainment

Participants were followed until last contact or death as assessed during April 2012, whichever occurred first. Date and cause of death, classified by International Classification of Diseases (ICD) codes version 9, were identified through annual vital status surveillance of all patients in the registry, conducted by MDCSS [22]. ICD codes 174.0-174.9 represented breast cancer deaths and other ICD codes represented death from causes other than breast cancer referred henceforward as other-cause mortality.

Statistical Analysis

Racial differences between continuous variables were assessed using Student t-test and between categorical variables were assessed by Pearson χ^2 or by Fisher's exact test when counts were small. Racial differences in sample medians were assessed using the Wilcoxon Rank Sum test. Kaplan-Meier plots were used to examine the association between functional limitations and mortality and P values for log-rank tests are provided in the **Appendix**. Cox proportional hazards models with time since diagnosis as the time scale were employed to estimate the association between measures of functional limitation and other-cause and breast cancer mortality [23]. In multivariable models, interaction terms were considered. Risk was expressed as a hazard ratio (HR) and 95% confidence interval (CI). The proportionality of hazards assumption was assessed using Schoenfeld residuals [24]. These tests revealed significant departures from proportionality. Therefore, models were stratified by age at breast cancer diagnosis. For analyses involving death from breast cancer, participants who died from other causes were removed from the cohort at the time of their death and vice versa. Treatment, tumor stage, tumor size, node involvement, race, BMI, financial adequacy, education, smoking status, and period of entry were considered as potential confounders in all multivariate analyses. To evaluate effect modification we conducted analyses separately for subgroups defined by BMI (<25, 25-30, >30) at the baseline interview and stage of breast cancer (local, regional or remote) at diagnosis. We combined women in the regional and remote categories due to the small number of respondents with remote disease (n=55). The type I error was set at .05 and all reported *P*-values are two-sided. Analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC) and R version 2.15.

RESULTS

The demographic and clinical characteristics of African-American (n=162; 16.6%) and white women (n=813; 83.3%) with breast cancer are presented in **Table 1**. Overall, the median follow-up time was 11.0 years (interquartile range [IQ]: 4.5-22.4 years). Median follow-up was significantly shorter for African-American women than their white counterparts (median =9.0 years [IQ: 3.0-19.0] vs. 12.0 [IQ: 4.8-22.7] years, P=0.0003). Among those who survived, African-American women (n=28) and white women (n=193) had similar follow-up (median =24.3 years vs. 24.4 years, P=0.07), which suggests that the difference in median survival between African-American and white women is due to increased mortality among African-American women. During this period, there were 753 deaths; 317 were due breast cancer and 436 were due to other causes. Slightly more African-American women died of breast cancer than white women (37.7% vs. 31.5%, P=0.13). There were no racial differences in the proportion of other-cause deaths (44.4% vs. 44.8%, P=0.94). The distribution of age was also similar in both groups. Compared to white women, African-American women had significantly fewer years of education (24.7% vs. 28.3% respectively had ≥12 years of education, P<0.0001), greater mean BMI (28.2 kg/m^2 vs. 25.9 kg/m^2, P<0.0001), and fewer reported adequate financial resources (66.7% vs. 86.0% respectively, P<0.0001). African-American women were less likely than their white counterparts to have localized disease (43.8% vs. 55.6% respectively, P=0.01) at the time of breast cancer diagnosis. Additionally, African-American women were more likely to have regional disease (48.1% vs. 39.2% respectively, P=0.04), receive no surgery (3.7% vs. 1.4% respectively, P=0.04), and have larger tumors, with mean tumor sizes of 38.2 (SD=26.2) and 32.8 (SD=24.7) millimeters for African-American and white women respectively (P=0.01).

The distributions of summary measures of functional limitations overall and by race are presented in **Table 1** and distributions of specific functional limitations are presented in **Figures**

1a and **1b.** At three months after breast cancer diagnosis, African-American women were more likely to report any functional limitations (83.3% vs. 67.3%, P<0.0001) and a greater number of functional limitations than their white counterparts (mean 2.8 [SD=2.3] and 2.1 [SD=2.3], P=0.0003). African-Americans were more likely than whites to report difficulty in pushing or pulling large objects (66.1% vs. 48.0%, P<0.0001), lifting less than 10 pounds (33.3% vs. 19.3%, P<0.0001), lifting more than 10 pounds (62.4% vs. 42.9%, P<0.0001), going up or down a flight of stairs (17.3% vs. 11.7%, P=0.05), and walking half a mile (29.6% vs. 22.1%, P=0.04). In addition to having a greater mean increase in the number of functional limitations during the first year after diagnosis (0.6 [SD=1.4] vs. 0.4 [SD=0.9], P=0.03), a larger proportion of African-American women reported difficulty going up or down a flight of stairs at month 12 but not month 3 (16.7% vs. 9.0%, P=0.003).

Other-cause mortality

Comparing white women with versus without functional limitations, Kaplan-Meier plots show considerably shorter other-cause survival for those with functional limitations (**Figure 2a**, P for log-rank test <0.0001, **Appendix**). Overall, African-American women with or without functional limitations have shorter survival than their white counterparts. Borderline statistically significant differences were observed in the survival curves of African-American women with functional limitations and their white counterparts (P for log-rank test=0.06). Difficulties in pushing or pulling large objects (HR=1.34, 95% CI 1.04-1.73), writing or handling small objects (HR=1.56, 95% CI 1.00-2.44), walking half a mile (HR=1.60, 95% CI 1.19-2.14), each unit increase in the number of self-reported functional limitations (HR=1.08, 95% CI 1.03-1.14), as well as experiencing any functional limitation (HR=1.47, 95% CI 1.13-1.91) were all associated with statistically significant increases in the risk of other-cause mortality (**Table 2**). Functional

decline was not associated with other-cause mortality. When evaluating effect modification by stage, we found that the number of functional limitations (HR=1.11, 95% CI 1.03-1.19) as well as 0 vs. ≥1 functional limitations (HR=1.46, 95% CI 1.05-2.03) were significantly associated with other-cause mortality in women with localized disease but not in those with regional or remote disease, whereas functional decline was associated with increased risk of other-cause mortality in women with regional and remote disease (HR=1.61, 95% CI 1.03-2.52), but not in those with localized disease (**Table 3**).

Breast cancer-specific mortality

Kaplan-Meier plots of breast cancer survival indicate that African-American women had poorer survival than white women (**Figure 2b**, **Appendix**). Furthermore, African-American women with functional limitations had significantly poorer survival than those without limitations (P for log-rank test=0.05). In multivariate models, we found no evidence of an association between any of the measures of functional limitations and breast cancer-specific mortality in this group (**Table 2**). On the other hand, each unit of functional decline (HR=1.17, 95% CI 1.05-1.31) and decline in the ability to sit ≥1 hour (HR=2.06, 95% CI 1.13-3.76) were both significantly associated with increased risk of breast cancer mortality. Each unit increase in the number of functional limitations was positively associated with other-cause mortality in overweight (BMI 25-30; HR=1.17, 95% CI 1.05-1.31) and obese women (BMI>30; HR=1.48, 95% CI 1.09-2.02), but not in women of normal weight (BMI<25; HR=1.13, 95% CI 0.94-1.36) (**Table 3**). Functional decline was positively associated with breast cancer mortality in obese women (HR=3.05, 95% CI 1.32-7.03).

DISCUSSION

We found that the presence of functional limitations after breast cancer diagnosis, including difficulties in mobility (walking half a mile) and in upper-body limitations (pushing or pulling large objects, writing or handling small objects) were associated with statistically significant increases in the risk of other-cause mortality in this biracial cohort of breast cancer survivors. Overall, functional limitations were more prevalent among African-American women. Race was a significant predictor of mortality in univariate models, but the association was no longer significant in covariate-adjusted models. These findings suggest that factors other than functional limitations are responsible for racial disparities in the survival of women with breast cancer. In evaluating whether the effect of functional limitations varies across strata of breast cancer stage at diagnosis, we found that the presence of functional limitations was statistically significantly associated with other-cause mortality in women with localized disease, but not in women with regional and remote disease. Conversely, functional decline was associated with increased risk of other-cause mortality in women with regional and remote disease, but not in women with localized disease. Analyses stratified by BMI revealed that the number of functional limitations was positively associated with other-cause mortality in overweight and obese women, but not in women of normal weight. Each unit of functional decline and decline in lower-body function (the ability to sit for an hour or longer) were both significantly associated with increased risk of breast cancer mortality. Functional decline was positively associated with breast cancer mortality in obese women. These findings underscore the prognostic role of obesity among breast cancer survivors.

This study extends earlier work that reported on diminished quality of life and self-reported functional limitations as predictors of decreased overall and non-breast cancer survival [2 25] to

show that limitations in lower body function and any functional decline during the first year after breast cancer diagnosis are strong predictors of breast cancer mortality. We found that functional decline has prognostic value for breast cancer independently of other prognostic factors and comorbidity; the impact of functional decline during the first year following breast cancer diagnosis is stronger in women with regional and remote disease. To our knowledge, this is the first study to evaluate the association of both individual limitations and functional decline with survival among breast cancer patients. Our findings underscore the predictive value of comprehensive measures of functional limitations.

Biological mechanisms by which functional limitations affect survival of breast cancer patients are not well understood. Chronic inflammation has been between linked to diminished physical functioning and disability in populations of older adults [26-31] and may underlie the observed association of functional limitations with mortality. Functional limitations and cancer may synergistically increase inflammation resulting in disease progression and mortality. In this study, we have shown that functional limitations differentially impact breast cancer-specific and other-cause mortality. Specifically, we observed that functional limitations measured at baseline predicted other-cause mortality, particularly among non-obese women and those with localized disease. On the other hand, functional decline was associated with breast cancer-specific mortality, particularly among overweight and obese women. Prior to probing potential mechanisms linking physical functioning and cause-specific mortality, these findings should be validated in other cohorts of breast cancer survivors with employing measures of functional limitations and other covariates, to verify the nature of the association between various aspects of physical functioning and cause-specific mortality. Identifying populations most likely to benefit

from targeted interventions to enhance functional status is the first step toward improving outcomes following breast cancer diagnosis.

In addition to our inability to address the underlying biological mechanisms, another important limitation of this study is that the majority of respondents were treated with partial or radical mastectomy, which is no longer the standard of care for early stage breast cancer. The currently recommended standard of care for this population consisting of radiation and segmental mastectomy or lumpectomy may have less impact on function. Modern surgical techniques may also reduce the functional impact of breast cancer surgery. Furthermore, the observed patterns of functional limitations in this study may have been affected by the fact that a relatively small number of participants received adjuvant chemotherapy or hormone therapy. Although the self-reported nature of functional limitations in this study may be subject to bias, self-reported functional limitations have been shown to correlate with performance-based measures[10]. Another limitation of the current study is our inability to compare whether women with breast cancer have a similar burden of functional limitations as women without breast cancer, and whether the impact of functional limitations on other-cause mortality differs in women with and without breast cancer.

The strengths of the study include comprehensive measures of functional limitations and decline, a prospective population-based cohort design, a relatively large set of white and African-American participants, a long follow-up, and our ability to take into account multiple covariates in the tumor-related, lifestyle and socio-demographic domains. Since women in this study were identified through a large regional population-based surveillance program, our findings may apply to wider audiences than studies in which subjects were drawn from academic settings.

Bias due to loss of follow-up was minimized because mortality status was ascertained annually for all the patients in the registry.

In summary, our findings indicate that functional limitations and functional decline during the first year following breast cancer diagnosis are associated with the breast cancer-specific and other-cause mortality of women with breast cancer.

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Tables and legends for figures

Table 1: Characteristics of the study group overall and by race

	Overall N = 975	African-American N = 162	White N = 813	P value
Age at diagnosis, mean ± SD	63 ± 12.4	62.5 ± 12.6	63.1 ± 12.4	0.59
Follow-up (years), Median (Q1, Q3)	11 (4.5,22.4)	9 (3,19)	12 (4.8,22.7)	0.0003
Financial adequacy	807 (82.8)	108 (66.7)	699 (86)	<.0001
Highest level of educational attainment, *N (%)*				
Less than high-school	375 (38.5)	89 (54.9)	286 (35.2)	<.0001
High-school	330 (33.8)	33 (20.4)	297 (36.5)	
College	210 (21.5)	32 (19.8)	178 (21.9)	
Graduate	60 (6.2)	8 (4.9)	52 (6.4)	
Body mass index (kg/m^2), mean ± SD	26.3 ± 5.3	28.2 ± 5.4	25.9 ± 5.1	<.0001
Stage, N *(%)*				
Local	523 (53.6)	71 (43.8)	452 (55.6)	0.01
Regional	397 (40.7)	78 (48.1)	319 (39.2)	0.04
Remote	55 (5.6)	13 (8)	42 (5.2)	0.15
Smoking, N *(%) current smokers*	195 (20)	37 (22.8)	158 (19.4)	0.32
Breast cancer treatment, N *(%)*				
No surgery	17 (1.7)	6 (3.7)	11 (1.4)	0.04
Partial mastectomy	194 (19.9)	29 (17.9)	165 (20.3)	0.49
Modified radical mastectomy	760 (77.9)	126 (77.8)	634 (78)	0.95
Number of lymph nodes involved, N *(%)*				
0	443 (45.4)	60 (37)	383 (47.1)	0.10
1-3	302 (31)	57 (35.2)	245 (30.1)	
≥4	39 (4)	10 (6.2)	29 (3.6)	
Tumor Size (mm), mean ± SD	33.7 ± 25	38.2 ± 26.2	32.8 ± 24.7	0.01
Comorbidity index, mean ± SD	2.2 ± 1.5	2.2 ± 1.6	2.2 ± 1.5	0.91
Functional limitations at 3 months after breast cancer diagnosis				
No. functional limitations, mean ± SD	2.2 ± 2.3	2.8 ± 2.3	2.1 ± 2.3	0.0003
≥1 functional limitation, N (%)	682 (69.9)	135 (83.3)	547 (67.3)	<.0001
Functional decline between baseline and 12 months				
No. functional limitation at month 12 and not 3, mean ± SD	0.4 ± 1	0.6 ± 1.4	0.4 ± 0.9	0.03
≥1 additional functional limitation reported at month 12, N (%)	212 (21.7)	36 (22.2)	176 (21.6)	0.87

Mortality, *N (%)*				
All-cause	753 (77.3)	133 (82.6)	620 (76.3)	0.08
Breast cancer-specific	317 (32.5)	61 (37.7)	256 (31.5)	0.13
Other-cause	436 (44.7)	72 (44.4)	364 (44.8)	0.94

Table 2: Hazard ratios (and 95% confidence intervals) of functional limitations for mortality *

Covariate	Other Cause Mortality (No. deaths = 436)		Breast Cancer Mortality (No. deaths = 317)	
	Baseline	**Decline**	**Baseline**	**Decline**
Model 1				
African-American	1.23 (0.91, 1.66)	1.19 (0.88, 1.62)	1.04 (0.76, 1.44)	1.08 (0.78, 1.49)
Model 2				
African-American	1.19 (0.87, 1.62)	1.19 (0.88, 1.62)	1.12 (0.81, 1.55)	1.08 (0.78, 1.49)
Difficulty pushing/pulling large objects (yes/no)	1.34 (1.04, 1.73)	0.98 (0.67, 1.43)	0.77 (0.58, 1.03)	1.41 (0.93, 2.13)
Difficulty stooping/crouching/kneeling (yes/no)	1.02 (0.77, 1.35)	0.97 (0.65, 1.45)	1.39 (0.99, 1.94)	0.94 (0.56, 1.57)
Difficulty lifting less than 10 pounds (yes/no)	0.92 (0.68, 1.25)	0.91 (0.53, 1.56)	1.05 (0.72, 1.53)	1.27 (0.65, 2.48)
Difficulty lifting ≥10 pounds (yes/no)	0.99 (0.75, 1.30)	1.07 (0.71, 1.60)	0.78 (0.56, 1.07)	1.20 (0.76, 1.89)
Difficulty extending arm above shoulder level (yes/no)	0.97 (0.72, 1.31)	0.94 (0.56, 1.58)	0.85 (0.58, 1.23)	0.92 (0.49, 1.76)
Difficulty writing/handling small objects (yes/no)	1.56 (1.00, 2.44)	0.47 (0.22, 1.03)	1.61 (0.95, 2.73)	1.19 (0.53, 2.68)
Difficulty standing more than 15 minutes (yes/no)	0.81 (0.58, 1.13)	1.33 (0.87, 2.02)	0.91 (0.62, 1.35)	1.58 (0.96, 2.62)
Difficulty sitting more than an hour (yes/no)	0.77 (0.49, 1.22)	1.75 (0.99, 3.09)	1.04 (0.63, 1.73)	2.06 (1.13, 3.76)
Difficulty going up/down a flight of stairs (yes/no)	1.29 (0.93, 1.78)	1.18 (0.82, 1.69)	1.07 (0.70, 1.63)	0.61 (0.37, 1.01)
Difficulty walking half a mile (yes/ no)	1.60 (1.19, 2.14)	1.34 (0.90, 2.00)	1.24 (0.88, 1.77)	1.32 (0.82, 2.13)
Model 3				
African-American	1.22 (0.90, 1.65)	1.19 (0.88, 1.61)	1.05 (0.76, 1.44)	1.01 (0.73, 1.40)
Functional limitations (continuous)	1.08 (1.03, 1.14)	1.10 (1.00, 1.21)	0.99 (0.93, 1.05)	1.17 (1.05, 1.31)
Model 4				
African-American	1.17 (0.87, 1.59)	1.21 (0.90, 1.63)	1.08 (0.78, 1.50)	1.04 (0.75, 1.43)
Functional limitations (≥1 vs. 0)	1.47 (1.13, 1.91)	1.17 (0.92, 1.50)	0.75 (0.56, 0.98)	1.26 (0.94, 1.69)

*Models were stratified by age at breast cancer diagnosis and additionally adjusted for stage of comorbidity, breast cancer, treatment, body mass index, financial adequacy, education, smoking, positive lymph node involvement, tumor size at diagnosis, and period of study entry.

Table 3: Hazard ratios (and 95% confidence intervals) of functional limitations for mortality stratified by tumor stage and body mass index*

	Other Cause Mortality (No. deaths = 436)		Breast Cancer Mortality (No. deaths = 317)	
	Baseline	**Decline**	**Baseline**	**Decline**
Stage of breast cancer at diagnosis*				
Local, N=523	*No. of deaths = 274*		*No. of deaths = 93*	
Functional limitations (continuous)	1.11 (1.03, 1.19)	1.07 (0.94, 1.23)	1.04 (0.92, 1.17)	1.16 (0.97, 1.38)
Functional limitations (≥1 vs. 0)	1.46 (1.05, 2.03)	1.06 (0.75, 1.49)	1.30 (0.76, 2.23)	1.02 (0.59, 1.77)
Regional and remote, N=452	*No. of deaths = 162*		*No. of deaths = 224*	
Functional limitations (continuous)	1.03 (0.94, 1.14)	1.19 (1.00, 1.43)	1.02 (0.94, 1.10)	1.08 (0.92, 1.26)
Functional limitations (≥1 vs. 0)	1.58 (0.90, 2.75)	1.61 (1.03, 2.52)	0.66 (0.47, 0.93)	1.19 (0.82, 1.73)
Body mass index at baseline, (kg/m^2)†				
<25, N=454	*No. of deaths = 210*		*No. of deaths = 128*	
Functional limitations (continuous)	1.11 (1.01, 1.22)	1.12 (0.94, 1.32)	1.01 (0.90, 1.14)	1.13 (0.94, 1.36)
Functional limitations (≥1 vs. 0)	1.80 (1.14, 2.84)	1.45 (0.93, 2.27)	0.74 (0.46, 1.18)	1.00 (0.57, 1.73)
25-30, N=323	*No. of deaths = 148*		*No. of deaths = 109*	
Functional limitations (continuous)	1.07 (1.02, 1.13)	1.10 (1.00, 1.21)	0.99 (0.93, 1.06)	1.17 (1.05, 1.31)
Functional limitations (≥1 vs. 0)	1.48 (1.13, 1.94)	1.24 (0.95, 1.60)	0.71 (0.54, 0.95)	1.28 (0.94, 1.73)
>30, N=198	*No. of deaths = 78*		*No. of deaths = 80*	
Functional limitations (continuous)	0.78 (0.60, 1.02)	1.09 (0.68, 1.76)	1.08 (0.92, 1.27)	1.48 (1.09, 2.02)
Functional limitations (≥1 vs. 0)	0.62 (0.18, 2.12)	2.15 (0.70, 6.60)	1.50 (0.61, 3.66)	3.05 (1.32, 7.03)

*Models were stratified by age at breast cancer diagnosis and additionally adjusted for race, comorbidity, breast cancer treatment, body mass index, financial adequacy, education, smoking, positive lymph node involvement, tumor size at diagnosis, and period of study entry.

†Models were stratified by age at breast cancer diagnosis and additionally adjusted for race, comorbidity, breast cancer stage, treatment, financial adequacy, education, smoking, positive lymph node involvement, tumor size at diagnosis, and period of study entry.

Appendix: P-values for the log-rank tests comparing the survival distributions in figures 2a and 2b, by comparison group

Comparison Groups	Other Cause Survival (Figure 2a)	Breast Cancer Survival (Figure 2b)
African-American women with ≥1 functional limitations vs. African-American women without functional limitations	<.0001	0.50
African-American women with ≥1 functional limitations vs. white women with ≥1 functional limitations	0.06	0.05
African-American women without functional limitations vs. white women without functional limitations	0.15	0.20
African-American women without functional limitations vs. white women with ≥1 functional limitations	0.84	0.33
White women with ≥1 functional limitations vs. white women without functional limitations	<.0001	0.50

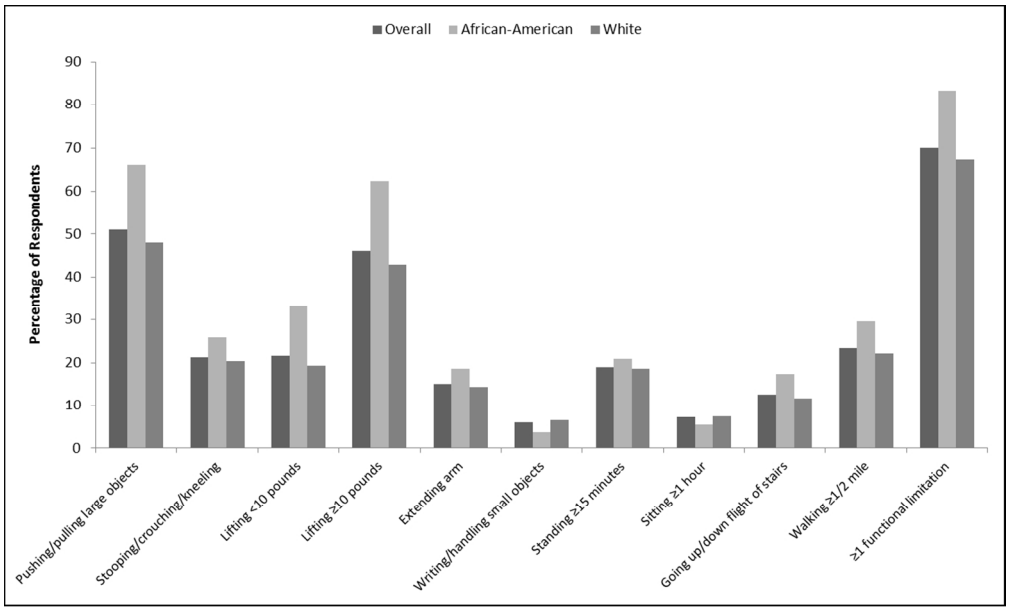

Figure 1a: Distribution of functional limitations reported at 3 months following breast cancer diagnosis

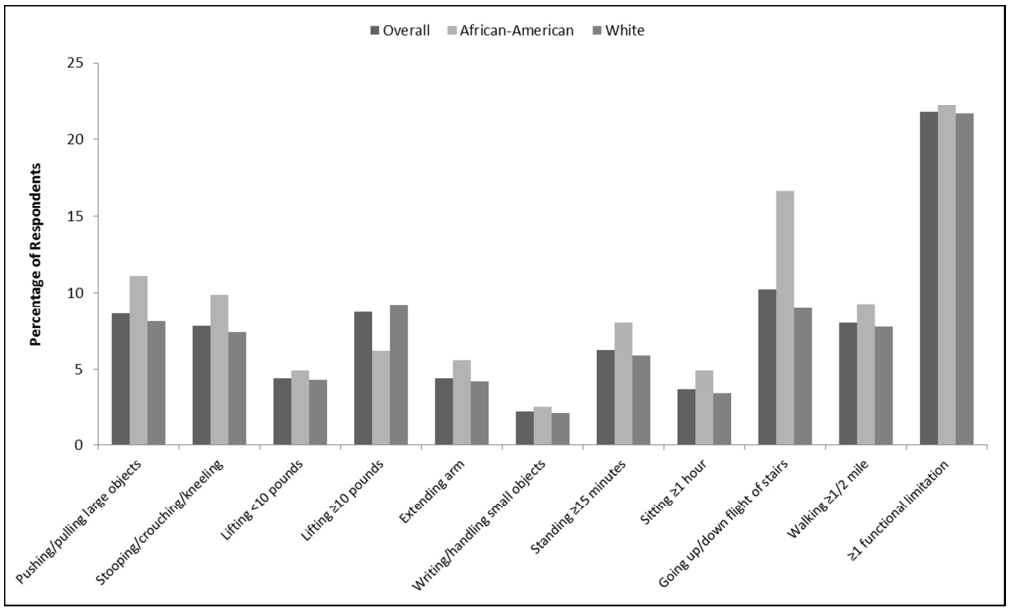

Figure 1b: Distribution of functional decline between the 3 and 12 months following breast cancer diagnosis

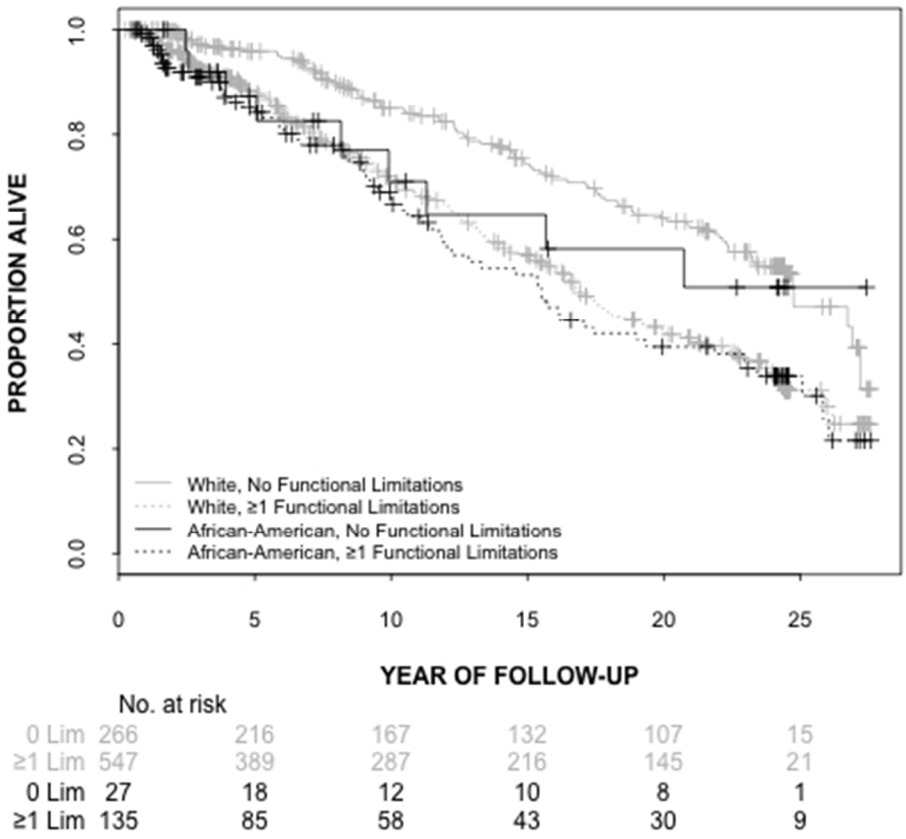

Figure 2a: Kaplan-Meier estimates of other-cause survival by race and category of functional limitations (0 vs. ≥ 1)
169x169mm (72 x 72 DPI)

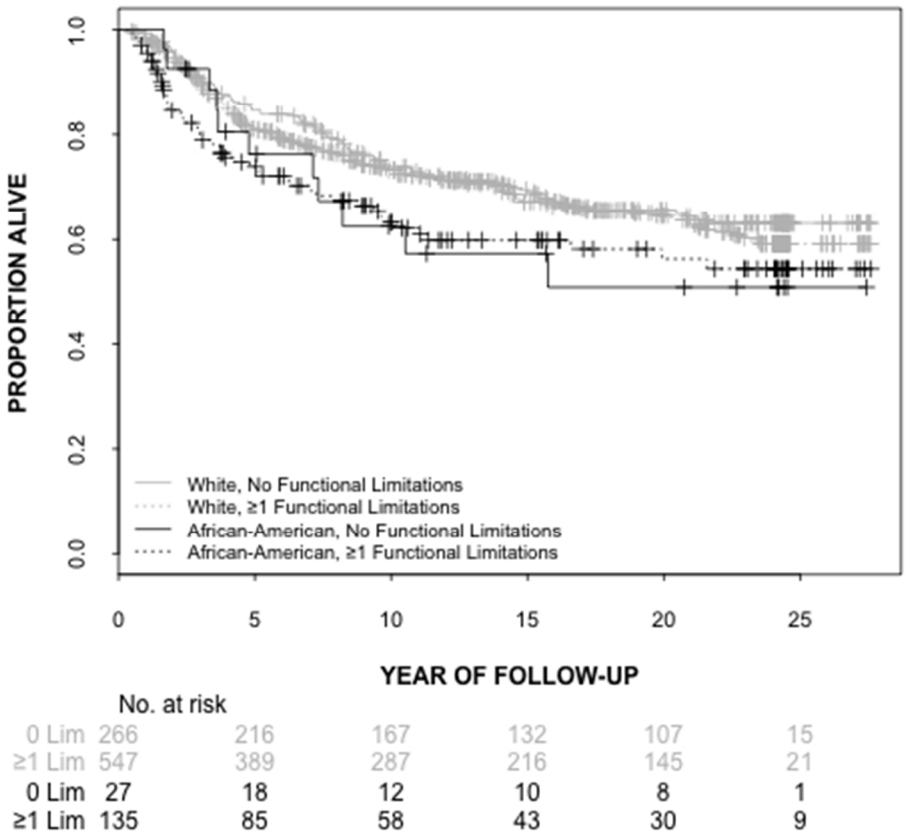

Figure 2b: Kaplan-Meier estimates of breast cancer survival by race and category of functional limitations (0 vs. ≥ 1)
169x169mm (72 x 72 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **A description of the study design is included in the abstract.**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **The abstract summarizes findings, and implications**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **We explain the scientific background and rationale in page 5 of the main document.**
Objectives	3	State specific objectives, including any pre-specified hypotheses **Have stated our hypothesis in pages 5, 6.**
Methods		
Study design	4	Present key elements of study design early in the paper **Elements of study design are presented in the "Study Population" section of methods.**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **This information is presented in the "Study Population" section of methods**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Eligibility criteria is also presented in the "Study Population" section.**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **Does not apply to our study.**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Exposures are described in the section "Functional limitations". Outcome is described in section "Endpoint Ascertainment". Potential confounders are listed under the heading "Covariates".**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **We have done so throughout the "Methods" section.**
Bias	9	Describe any efforts to address potential sources of bias. **Discussed in methods.**
Study size	10	Explain how the study size was arrived at **Exclusion criteria are described in the "Methods" section.**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **A detailed description of statistical methods is provided in the manuscript.**
		(*b*) Describe any methods used to examine subgroups and interactions **Effect modification was evaluated by analysing subgroups separately. A detailed description is provided in the "Methods" section.**
		(*c*) Explain how missing data were addressed **No data were missing.**
		(*d*) If applicable, explain how loss to follow-up was addressed

		A description is provided in the "Methods" section.
		(*e*) Describe any sensitivity analyses **None were conducted.**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed**:** **This information is provided in the "Study Population" section.**
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Table 1 presents this data.**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount) **Summarized in Table 1**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Reported in Tables 2 and 3**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Legends are provided for Tables 2 and 3 along with a listing of the confounders.**
		(*b*) Report category boundaries when continuous variables were categorized **Explained categories used in methods.**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Table 3presents findings for subgroup analyses.**
Discussion		
Key results	18	Summarise key results with reference to study objectives **We summarise key findings in the first paragraph of the discussion section.**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **We list a number of limitations in the discussion section.**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results **We provide a discussion of generalisability.**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Sources of funding and the role of funders are listed in the main document.**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Title: The Impact of Functional Limitations on Long-term Outcomes among African-American and White Women with Breast Cancer: A Cohort Study

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Running Title: Functional Limitations among Breast Cancer Survivors

Keywords: Racial disparity, breast cancer, functional limitations, mortality, survival, cohort study

Text Word Count: 3152; Abstract Word Count: 309; Tables: 3; Figures: 2; References: 30

ABSTRACT

Objectives: We examined the impact of functional limitations and functional decline during the first year following breast cancer diagnosis respectively on the risk of mortality from breast cancer and other causes among African-American and white women.

Design: The Health and Functioning in Women ~~(HFW)~~ cohort study.

Setting: Detroit, Michigan, U.S.A.

Participants: A total of 162 African-American and 813 white women aged 40-84 years with newly diagnosed breast cancer identified through the Metropolitan Detroit Cancer Surveillance System ~~(MDCSS)~~ over a 7-month period between 1984 and 1985 and followed for up to 28 years (median ~~follow-up =~~ 11.0 years).

Outcome measures: Risk of mortality from breast cancer and other causes.

Results: Statistically significant increases in the risk of other-cause mortality were found for each unit increase in the number of self-reported functional limitations (HR=1.08, 95% CI 1.03-1.14), 0 versus ≥1 functional limitations (HR=1.47, 95% CI 1.13-1.91), difficulty in pushing or pulling large objects (HR=1.34, 95% CI 1.04-1.73), writing or handling small objects (HR=1.56, 95% CI 1.00-2.44), and walking half a mile (HR=1.60, 95% CI 1.19-2.14). Functional limitations and decline did not explain racial disparities in the survival of this cohort. Functional decline was associated with increased risk of other-cause mortality in women with regional and ~~distant~~ remote disease but not in women with localized disease. Whereas measures of functional limitation were not associated with breast cancer-specific mortality, each unit of functional decline (HR=1.17, 95% CI 1.05-1.31)~~(HR=1.34, 95% CI 1.04-1.73)~~ and decline in the ability to sit ≥1 hour (HR=~~1.17~~2.06, 95% CI ~~1.05-1.31~~1.13-3.76) were associated with increased risk of

breast cancer-specific mortality. Measures of functional decline were associated with increased risk of breast-cancer mortality in overweight and obese women, but not in women of normal weight.

Conclusions: Whereas functional limitations were associated with increased risk of other cause mortality, functional decline was associated with increased risk of breast cancer mortality.

ARTICLE SUMMARY

Article Focus:

- The purpose of this study was to assess the long-term prognostic role of functional limitations and functional decline after breast cancer diagnosis in a cohort of African-American and white breast cancer survivors.
- We evaluated whether disparities in the survival of African-American and white women with breast cancer are accounted in part by functional limitations.
- We examined the extent to which the impact of functional limitations on mortality differed as a function of tumor stage and body mass index (BMI).

Key Messages:

- Functional limitations were associated with increased risk of other-cause mortality in this study; functional decline was associated with increased risk of breast cancer-specific mortality.
- Decline in functional status over the first year after breast cancer diagnosis is associated with increased risk of breast cancer-specific mortality.
- Whereas the impact of functional decline on other-cause mortality differs as a function of tumor stage, its impact on breast cancer-specific mortality differs by body mass index (BMI).
- Functional limitations did not explain survival disparities among African-American and white women with breast cancer.

Strengths and Limitations:

- This study used comprehensive measures of functional limitations and decline, a prospective population-based cohort design, a relatively large set of white and African-

American participants, a long follow-up, and multiple covariates in the tumor-related, lifestyle and socio-demographic domains.

- Functional limitations were self-reported and the majority of respondents were treated with partial or radical mastectomy, which is no longer the standard of care for early stage breast cancer.

Abbreviations and Acronyms:

HFW: Health and Functioning in Women study

BMI: body mass index

HR: hazard ratio

95% CI: 95% confidence interval

MDCSS: Metropolitan Detroit Cancer Surveillance System

kg: kilograms

m^2: meters squared

ICD: International Classification of Diseases

IQ: interquartile range

LACE: Life after Cancer Epidemiology study

INTRODUCTION

Functional limitations at the time of breast cancer diagnosis and following initial treatment have been associated with a number of adverse outcomes among breast cancer survivors [1-4]. Summary measures of physical functioning have been previously evaluated among breast cancer survivors [2 5 6]. Yet the prognostic value of individual limitations versus summary measures of physical functioning and functional decline remains poorly understood. Primary treatment causes functional decline in some breast cancer patients[7-9], and while most recover, some older women do not and may decline even further[10 11]. While functional decline in the first two years after breast cancer diagnosis has been related to 10-year survival among women with breast cancer [12], its impact on longer term survival has not been evaluated. It is also unclear whether any differences in physical functioning exist among population subgroups. For example, older African-American breast cancer patients have been shown to have a disproportionately increased comorbidity burden compared to their white counterparts but it is unknown whether they also have more limitations in physical functioning. A better understanding of the role of functional limitations and decline may provide opportunities to reduce mortality among breast cancer survivors through targeted interventions within high-risk populations[13].

In this study of the long-term prognostic role of functional limitations and functional decline, we considered death from breast cancer and other causes in a cohort of African-American and white breast cancer survivors from the Health and Functioning in Women (HFW) study [5]. A wide age range, the inclusion of both African-American and white women, and a median follow up of 11 years make this cohort particularly suitable for examining racial disparities and the long-term effect of functional limitations and decline while taking into account a wide range of clinical, lifestyle-related, and socio-demographic prognostic factors. We hypothesized that the presence

of functional limitations in the first few months after breast cancer diagnosis and the subsequent decline in functional status over the first year are associated with increased risk of mortality. As disparities in the survival of African-American and white women continue to exist[14 15], we also wished to evaluate whether they could be accounted in part by functional limitations. Obesity is a significant contributor to survival disparities among breast cancer patients [16] and is an important prognostic factor in postmenopausal women[17 18]. Furthermore, although functional limitations have been associated with tumor stage[19], the extent to which disease severity affects the impact of functional limitations on mortality is not well understood[2]. Therefore, we also examined the extent to which the impact of functional limitations on mortality differed as a function of tumor stage and body mass index (BMI).

METHODS

Study Population

The Health and Functioning in Women (HFW) study used in the present analysis has been previously described[5 6]. Briefly, the HFW study was established in 1984 in the Detroit metropolitan area to assess the health, functional, and psychosocial status of women following breast cancer diagnosis. A total of 1,011 eligible participants ages 40-84 with newly diagnosed, histologically confirmed, primary invasive breast cancer identified through the Metropolitan Detroit Cancer Surveillance System (MDCSS) at the Michigan Cancer Foundation, now the Barbara Ann Karmanos Cancer Institute, within 4 weeks of diagnosis and were interviewed in two cohorts. The first cohort consisted of 571 participants ages 55-84, that were identified over a 7-month period between 1984 and 1985; of these, 463 (81.1%) were successfully interviewed between 2 and 4 months following diagnosis. A second cohort of 620 eligible cases, ages 40-54

and 74-84, was identified over a 7-month period between 1987 and 1988; 548 (88.4%) of these participants were successfully interviewed between 2 and 4 months after diagnosis, henceforth referred to as *the baseline interview* or *month 3 interview*. All participants were interviewed a second time approximately 9 months after the first interview, henceforth referred to as *month 12 interview*. The two cohorts were combined and 975 women, for whom complete data were available on all key variables, were included in this analysis. This study was approved by the Committee on Human Research at the University of California, San Francisco. Additionally, the HFW study was approved at the time of its inception by the Human Subjects Committee at the Michigan Cancer Foundation.

Functional Limitation Assessment

Respondents were asked at both 3 and 12 month interviews whether they experienced difficulty in performing any of the physical tasks described by Nagi: (i) pushing or pulling large objects, (ii) stooping, crouching, or kneeling, (iii) lifting objects weighing less than 10 pounds, (iv) lifting objects weighting more than 10 pounds, (v) reaching or extending arms above or below shoulder level, (vi) writing or handling small objects, (vii) standing longer than 15 minutes, (viii) sitting longer than an hour, (ix) going up or down a flight of stairs, (x) and walking half a mile [5 6 20]. A woman was considered to have a functional limitation if she reported that the task was completed with a lot of difficulty or avoided on doctor's orders[6]. In this analysis, we considered (a) the effect of individual functional limitations reported at the baseline interview, (b) the effect of the number of functional limitations reported at the 3 month interview as a continuous predictor, and (c) also the effect of a binary predictor indicating the presence of any functional limitation at the 3 month interview (≥1 functional limitations vs. 0) on mortality in order to evaluate a non-linear relationship. We also separately considered the association of three measures of functional

decline between the first and second interviews with mortality. These measures were (1) binary predictors of developing a specific functional limitation between the 3 and 12 month interviews, (2) the number of functional limitations first reported at the month 12 interview as a continuous predictor, and (3) a binary indicator of any newly reported function limitations (≥1 vs. 0), henceforth referred to as *functional decline*.

Covariates

The covariates used in this analysis were socio-demographic, lifestyle-related, and clinical prognostic factors that, based on the existing literature and *a priori* reasoning, could potentially confound associations between functional limitations and mortality outcomes. Age at diagnosis, breast cancer stage, breast cancer treatment, tumor size, and node involvement were obtained from the MDCSS file, while other variables were obtained from interviews. In analyses, age was used as a continuous variable. Race was coded as either African-American or white. Years of education were recoded into 4 categories: less than high-school, high-school, college, and graduate. The dataset included a binary indicator of financial adequacy (0 for adequate and 1 for inadequate) that was based on self-reported current financial resources and whether they met the participant's needs[6]. BMI was calculated as weight in kilograms/height in meters squared, or kg/m^2, from self-reported weight and height at the baseline interview and used as continuous variable in multivariate models. Smoking status was self-reported and recoded as a binary indicator of whether the participant was a smoker at the time of the interview. A comorbidity index was constructed as the number of previously diagnosed conditions reported by the respondent at the baseline interview from a list of 23 conditions that included diabetes, hypertension, stroke, heart disease, gastrointestinal disease, liver conditions, and primary cancers

other than breast cancer, which according to the respondent currently caused some limitation in her activities [6].

Stage of breast cancer at diagnosis was coded as local, regional, or remote. In addition to information on surgery (no surgery, partial mastectomy, or modified radical mastectomy) ~~and type of adjuvant therapy (radiation or chemotherapy)~~ provided by the MDCSS files, physicians completed a supplementary survey regarding chemotherapy and hormonal therapy administered on an outpatient basis. However, adjuvant therapy utilization has been shown to be underreported in SEER registries[21], resulting in a small number of participants with evidence of chemotherapy and/or hormonal therapy treatment in addition to partial or radical mastectomy. Less than 30 women received no surgery. We combined ~~Data~~data from the ~~two sources~~ MDCSS files and physician surveys~~were combined~~ to create a two-level treatment variable (no surgery or partial mastectomy, and modified radical mastectomy). The log of the tumor size in millimeters was centered around its mean and used as a continuous variable. The number of positive lymph nodes involved was recoded into a three-level variable (0 nodes, 1-3 nodes, and ≥4 nodes).

Endpoint Ascertainment

Participants were followed until last contact or death as assessed during April 2012, whichever occurred first. Date and cause of death, classified by International Classification of Diseases (ICD) codes version 9, were identified through annual vital status surveillance of all patients in the registry, conducted by MDCSS [22]. ICD codes 174.0-174.9 represented breast cancer deaths and other ICD codes represented death from causes other than breast cancer referred henceforward as other-cause mortality.

Statistical Analysis

Racial differences between continuous variables were assessed using Student t-test and between categorical variables were assessed by Pearson χ^2 or by Fisher's exact test when counts were small. Racial differences in sample medians were assessed using the Wilcoxon Rank Sum test. Kaplan-Meier plots were used to examine the association between functional limitations and mortality and P values for log-rank tests are provided in the **Appendix**. Cox proportional hazards models ~~stratified by age at breast cancer diagnosis~~ with time since diagnosis as the time scale were employed to estimate the association between measures of functional limitation and other-cause and breast cancer mortality [23]. In multivariable models, interaction terms were considered. Risk was expressed as a hazard ratio (HR) and 95% confidence interval (CI). The proportionality of hazards assumption was assessed using Schoenfeld residuals [24]. These tests revealed ~~no~~ significant departures from proportionality. Therefore, models were stratified by age at breast cancer diagnosis. For analyses involving death from breast cancer, participants who died from other causes were removed from the cohort at the time of their death and vice versa. Treatment, tumor stage, tumor size, node involvement, race, BMI, financial adequacy, education, smoking status, and period of entry were considered as potential confounders in all multivariate analyses. To evaluate effect modification we conducted analyses separately for subgroups defined by BMI (<25, 25-30, >30) at the baseline interview and stage of breast cancer (local, regional or remote ~~or distant~~) at diagnosis. We combined women in the ~~distant~~ regional and remote categories due to the small number of respondents with ~~distant~~ remote disease (n=55). The type I error was set at .05 and all reported *P*-values are two-sided. Analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC) and R version 2.15.

RESULTS

The demographic and clinical characteristics of African-American (n=162; 16.6%) and white women (n=813; 83.3%) with breast cancer are presented in **Table 1**. Overall, the median follow-up time was 11.0 years (interquartile range [IQ]: 4.5-22.4 years). Median follow-up was significantly shorter for African-American women than their white counterparts (median =9.0 years [IQ: 3.0-19.0] vs. 12.0 [IQ: 4.8-22.7] years, P=0.0003). Among those who survived, African-American women (n=28) and white women (n=193) had similar follow-up (median =24.3 years vs. 24.4 years, P=0.07), which suggests that the difference in median survival between African-American and white women is due to increased mortality among African-American women. During this period, there were 753 deaths; 317 were due breast cancer and 436 were due to other causes. Slightly more African-American women died of breast cancer than white women (37.7% vs. 31.5%, P=0.13). There were no racial differences in the proportion of other-cause deaths (44.4% vs. 44.8%, P=0.94). The distribution of age was also similar in both groups. Compared to white women, African-American women had significantly fewer years of education (24.7% vs. 28.3% respectively had ≥12 years of education, P<0.0001), greater mean BMI (28.2 kg/m^2 vs. 25.9 kg/m^2, P<0.0001), and fewer reported adequate financial resources (66.7% vs. 86.0% respectively, P<0.0001). African-American women were less likely than their white counterparts to have localized disease (43.8% vs. 55.6% respectively, P=0.01) at the time of breast cancer diagnosis. Additionally, African-American women were more likely to have regional disease (48.1% vs. 39.2% respectively, P=0.04), receive no surgery (3.7% vs. 1.4% respectively, P=0.04), and have larger tumors, with mean tumor sizes of 38.2 (SD=26.2) and 32.8 (SD=24.7) millimeters for African-American and white women respectively (P=0.01).

The distributions of summary measures of functional limitations overall and by race are presented in **Table 1** and distributions of specific functional limitations are presented in **Figures**

1a and **1b.** At three months after breast cancer diagnosis, African-American women were more likely to report any functional limitations (83.3% vs. 67.3%, P<0.0001) and a greater number of functional limitations than their white counterparts (mean 2.8 [SD=2.3] and 2.1 [SD=2.3], P=0.0003). African-Americans were more likely than whites to report difficulty in pushing or pulling large objects (66.1% vs. 48.0%, P<0.0001), lifting less than 10 pounds (33.3% vs. 19.3%, P<0.0001), lifting more than 10 pounds (62.4% vs. 42.9%, P<0.0001), going up or down a flight of stairs (17.3% vs. 11.7%, P=0.05), and walking half a mile (29.6% vs. 22.1%, P=0.04). In addition to having a greater mean increase in the number of functional limitations during the first year after diagnosis (0.6 [SD=1.4] vs. 0.4 [SD=0.9], P=0.03),- a larger proportion of African-American women reported difficulty going up or down a flight of stairs at month 12 but not month 3 (16.7% vs. 9.0%, P=0.003).

Other-cause mortality

Comparing white women with versus without functional limitations, Kaplan-Meier plots show considerably shorter other-cause survival for those with functional limitations (**Figure 2a**, P for log-rank test <0.0001, **Appendix**). Overall, African-American women with or without functional limitations have shorter survival than their white counterparts. ~~However,~~Borderline statistically significant differences were observed in -the survival curves of African-American women with functional limitations ~~is not considerably different than that of~~and their white counterparts (P for log-rank test=0.06). Difficulties in pushing or pulling large objects (HR=1.34, 95% CI 1.04-1.73), writing or handling small objects (HR=1.56, 95% CI 1.00-2.44), walking half a mile (HR=1.60, 95% CI 1.19-2.14), each unit increase in the number of self-reported functional limitations (HR=1.08, 95% CI 1.03-1.14), as well as experiencing any functional limitation (HR=1.47, 95% CI 1.13-1.91) were all associated with statistically significant increases in the

risk of other-cause mortality (**Table 2**). Functional decline was not associated with other-cause mortality. When evaluating effect modification by stage, we found that the number of functional limitations (HR=1.11, 95% CI 1.03-1.19) as well as 0 vs. ≥1 functional limitations (HR=1.46, 95% CI 1.05-2.03) were significantly associated with other-cause mortality in women with localized disease but not in those with regional or ~~distant~~ remote disease, whereas functional decline was associated with increased risk of other-cause mortality in women with regional and ~~distant~~ remote disease (HR=1.61, 95% CI 1.03-2.52), but not in those with localized disease (**Table 3**).

Breast cancer-specific mortality

Kaplan-Meier plots of breast cancer survival indicate that African-American women had poorer survival than white women (**Figure 2b**, **Appendix**). Furthermore, African-American women ~~within racial groups women~~ with functional limitations had ~~slightly~~ significantly poorer survival than those without limitations (P for log-rank test=0.05). In multivariate models, we found no evidence of an association between any of the measures of functional limitations and breast cancer-specific mortality in this group (**Table 2**). On the other hand, each unit of functional decline (HR=1.17, 95% CI 1.05-1.31) ~~(HR=1.34, 95% CI 1.04-1.73)~~ and decline in the ability to sit ≥1 hour ~~(HR=1.17, 95% CI 1.05-1.31)~~ (HR=2.06, 95% CI 1.13-3.76) -were both significantly associated with increased risk of breast cancer mortality. Each unit increase in the number of functional limitations was positively associated with other-cause mortality in overweight (BMI 25-30; HR=1.17, 95% CI 1.05-1.31) and obese women (BMI>30; HR=1.48, 95% CI 1.09-2.02), but not in women of normal weight (BMI<25; HR=1.13, 95% CI 0.94-1.36) (**Table 3**). Functional decline was positively associated with breast cancer mortality in obese women (HR=3.05, 95% CI 1.32-7.03).

DISCUSSION

We found that the presence of functional limitations after breast cancer diagnosis, including difficulties in mobility (walking half a mile) and in upper-body limitations (pushing or pulling large objects, writing or handling small objects) were associated with statistically significant increases in the risk of other-cause mortality ~~compared to those with breast cancer without such limitations~~ in this biracial cohort of breast cancer survivors. Overall, functional limitations were more prevalent among African-American women. Race was a significant predictor of mortality in univariate models, but the association was no longer significant in covariate-adjusted models. These findings suggest that factors other than functional limitations are responsible for racial disparities in the survival of women with breast cancer. In evaluating whether the effect of functional limitations varies across strata of breast cancer stage at diagnosis, we found that ~~The~~ the presence of functional limitations was statistically significantly associated with other-cause mortality in women with localized disease, but not in women with regional and ~~distance~~ remote disease. Conversely, functional decline was associated with increased risk of other-cause mortality in women with regional and ~~distant~~ remote disease, but not in women with localized disease. ~~Each unit of functional decline and decline in lower-body function (the ability to sit for an hour or longer) were both significantly associated with increased risk of breast cancer mortality.~~ Analyses stratified by BMI revealed that the number of functional limitations was positively associated with other-cause mortality in overweight and obese women, but not in women of normal weight. Each unit of functional decline and decline in lower-body function (the ability to sit for an hour or longer) were both significantly associated with increased risk of breast cancer mortality. Functional decline was positively associated with breast cancer mortality

in obese women. These findings underscore the prognostic role of obesity among breast cancer survivors.

This study extends earlier work that reported on diminished quality of life and self-reported functional limitations as predictors of decreased overall and non-breast cancer survival [2 25] to show that limitations in lower body function and any functional decline during the first year after breast cancer diagnosis are strong predictors of breast cancer mortality. We found that functional decline has prognostic value for breast cancer independently of other prognostic factors and comorbidity; the impact of functional decline during the first year following breast cancer diagnosis is stronger in women with regional and remote disease. To our knowledge, this is the first study to evaluate the association of both individual limitations and functional decline with survival among breast cancer patients. Our findings underscore the predictive value of comprehensive measures of functional limitations.

Biological mechanisms by which functional limitations affect survival of breast cancer patients are not well understood. Chronic inflammation has been between linked to diminished physical functioning and disability in populations of older adults [26-31] and may underlie the observed association of functional limitations with mortality. Functional limitations and cancer may synergistically increase inflammation resulting in disease progression and mortality. In this study, we have shown that functional limitations differentially impact breast cancer-specific and other-cause mortality. Specifically, we observed that functional limitations measured at baseline predicted other-cause mortality, particularly among non-obese women and those with localized disease. On the other hand, functional decline was associated with breast cancer-specific mortality, particularly among overweight and obese women. Prior to probing potential mechanisms linking physical functioning and cause-specific mortality, these findings should be

validated in other cohorts of breast cancer survivors with employing measures of functional limitations and other covariates, to verify the nature of the association between various aspects of physical functioning and cause-specific mortality. Identifying populations most likely to benefit from targeted interventions to enhance functional status is the first step toward improving outcomes following breast cancer diagnosis.

In addition to our inability to address the underlying biological mechanisms, another important limitation of this study is that the majority of respondents were treated with partial or radical mastectomy, which is no longer the standard of care for early stage breast cancer. The currently recommended standard of care for this population consisting of radiation and segmental mastectomy or lumpectomy may have less impact on function. Modern surgical techniques may also reduce the functional impact of breast cancer surgery. Furthermore, the observed patterns of functional limitations in this study may have been affected by the fact that a relatively small number of participants received adjuvant chemotherapy or hormone therapy. Although the self-reported nature of functional limitations in this study may be subject to bias, self-reported functional limitations have been shown to correlate with performance-based measures[10]. Another limitation of the current study is our inability to compare whether women with breast cancer have a similar burden of functional limitations as women without breast cancer, and whether the impact of functional limitations on other-cause mortality differs in women with and without breast cancer.

The strengths of the study include comprehensive measures of functional limitations and decline, a prospective population-based cohort design, a relatively large set of white and African-American participants, a long follow-up, and our ability to take into account multiple covariates in the tumor-related, lifestyle and socio-demographic domains. Since women in this study were

identified through a large regional population-based surveillance program, our findings may apply to wider audiences than studies in which subjects were drawn from academic settings. Bias due to loss of follow-up was minimized because mortality status was ascertained annually for all the patients in the registry.

In summary, our findings indicate that functional limitations and functional decline during the first year following breast cancer diagnosis are associated with the breast cancer-specific and other-cause mortality of women with breast cancer.

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Tables and legends for figures

Table 1: Characteristics of the study group overall and by race

	Overall N = 975	African-American N = 162	White N = 813	P value
Age at diagnosis, mean ± SD	63 ± 12.4	62.5 ± 12.6	63.1 ± 12.4	0.59
Follow-up (years), Median (Q1, Q3)	11 (4.5,22.4)	9 (3,19)	12 (4.8,22.7)	0.0003
Financial adequacy	807 (82.8)	108 (66.7)	699 (86)	<.0001
Highest level of educational attainment, *N (%)*				
Less than high-school	375 (38.5)	89 (54.9)	286 (35.2)	<.0001
High-school	330 (33.8)	33 (20.4)	297 (36.5)	
College	210 (21.5)	32 (19.8)	178 (21.9)	
Graduate	60 (6.2)	8 (4.9)	52 (6.4)	
Body mass index (kg/m^2), mean ± SD	26.3 ± 5.3	28.2 ± 5.4	25.9 ± 5.1	<.0001
Stage, N *(%)*				
Local	523 (53.6)	71 (43.8)	452 (55.6)	0.01
Regional	397 (40.7)	78 (48.1)	319 (39.2)	0.04
Remote	55 (5.6)	13 (8)	42 (5.2)	0.15
Smoking, N *(%) current smokers*	195 (20)	37 (22.8)	158 (19.4)	0.32
Breast cancer treatment, N *(%)*				
No surgery	17 (1.7)	6 (3.7)	11 (1.4)	0.04
Partial mastectomy	194 (19.9)	29 (17.9)	165 (20.3)	0.49
Modified radical mastectomy	760 (77.9)	126 (77.8)	634 (78)	0.95
Number of lymph nodes involved, N *(%)*				
0	443 (45.4)	60 (37)	383 (47.1)	0.10
1-3	302 (31)	57 (35.2)	245 (30.1)	
≥4	39 (4)	10 (6.2)	29 (3.6)	
Tumor Size (mm), mean ± SD	33.7 ± 25	38.2 ± 26.2	32.8 ± 24.7	0.01
Comorbidity index, mean ± SD	2.2 ± 1.5	2.2 ± 1.6	2.2 ± 1.5	0.91
Functional limitations at 3 months after breast cancer diagnosis				
No. functional limitations, mean ± SD	2.2 ± 2.3	2.8 ± 2.3	2.1 ± 2.3	0.0003
≥1 functional limitation, N (%)	682 (69.9)	135 (83.3)	547 (67.3)	<.0001
Functional decline between baseline and 12 months				
No. functional limitation at month 12 and not 3, mean ± SD	0.4 ± 1	0.6 ± 1.4	0.4 ± 0.9	0.03
≥1 additional functional limitation reported at month 12, N (%)	212 (21.7)	36 (22.2)	176 (21.6)	0.87

Mortality, *N (%)*				
All-cause	753 (77.3)	133 (82.6)	620 (76.3)	0.08
Breast cancer-specific	317 (32.5)	61 (37.7)	256 (31.5)	0.13
Other-cause	436 (44.7)	72 (44.4)	364 (44.8)	0.94

Table 2: Hazard ratios (and 95% confidence intervals) of functional limitations for mortality *

Covariate	Other Cause Mortality (No. deaths = 436)		Breast Cancer Mortality (No. deaths = 317)	
	Baseline	**Decline**	**Baseline**	**Decline**
Model 1				
African-American	1.23 (0.91, 1.66)	1.19 (0.88, 1.62)	1.04 (0.76, 1.44)	1.08 (0.78, 1.49)
Model 2				
African-American	1.19 (0.87, 1.62)	1.19 (0.88, 1.62)	1.12 (0.81, 1.55)	1.08 (0.78, 1.49)
Difficulty pushing/pulling large objects (yes/no)	1.34 (1.04, 1.73)	0.98 (0.67, 1.43)	0.77 (0.58, 1.03)	1.41 (0.93, 2.13)
Difficulty stooping/crouching/kneeling (yes/no)	1.02 (0.77, 1.35)	0.97 (0.65, 1.45)	1.39 (0.99, 1.94)	0.94 (0.56, 1.57)
Difficulty lifting less than 10 pounds (yes/no)	0.92 (0.68, 1.25)	0.91 (0.53, 1.56)	1.05 (0.72, 1.53)	1.27 (0.65, 2.48)
Difficulty lifting ≥10 pounds (yes/no)	0.99 (0.75, 1.30)	1.07 (0.71, 1.60)	0.78 (0.56, 1.07)	1.20 (0.76, 1.89)
Difficulty extending arm above shoulder level (yes/no)	0.97 (0.72, 1.31)	0.94 (0.56, 1.58)	0.85 (0.58, 1.23)	0.92 (0.49, 1.76)
Difficulty writing/handling small objects (yes/no)	1.56 (1.00, 2.44)	0.47 (0.22, 1.03)	1.61 (0.95, 2.73)	1.19 (0.53, 2.68)
Difficulty standing more than 15 minutes (yes/no)	0.81 (0.58, 1.13)	1.33 (0.87, 2.02)	0.91 (0.62, 1.35)	1.58 (0.96, 2.62)
Difficulty sitting more than an hour (yes/no)	0.77 (0.49, 1.22)	1.75 (0.99, 3.09)	1.04 (0.63, 1.73)	2.06 (1.13, 3.76)
Difficulty going up/down a flight of stairs (yes/no)	1.29 (0.93, 1.78)	1.18 (0.82, 1.69)	1.07 (0.70, 1.63)	0.61 (0.37, 1.01)
Difficulty walking half a mile (yes/ no)	1.60 (1.19, 2.14)	1.34 (0.90, 2.00)	1.24 (0.88, 1.77)	1.32 (0.82, 2.13)
Model 3				
African-American	1.22 (0.90, 1.65)	1.19 (0.88, 1.61)	1.05 (0.76, 1.44)	1.01 (0.73, 1.40)
Functional limitations (continuous)	1.08 (1.03, 1.14)	1.10 (1.00, 1.21)	0.99 (0.93, 1.05)	1.17 (1.05, 1.31)
Model 4				
African-American	1.17 (0.87, 1.59)	1.21 (0.90, 1.63)	1.08 (0.78, 1.50)	1.04 (0.75, 1.43)
Functional limitations (≥1 vs. 0)	1.47 (1.13, 1.91)	1.17 (0.92, 1.50)	0.75 (0.56, 0.98)	1.26 (0.94, 1.69)

*Models were stratified by age at breast cancer diagnosis and additionally adjusted for stage of comorbidity, breast cancer, treatment, body mass index, financial adequacy, education, smoking, positive lymph node involvement, tumor size at diagnosis, and period of study entry.

Table 3: Hazard ratios (and 95% confidence intervals) of functional limitations for mortality stratified by tumor stage and body mass index*

	Other Cause Mortality (No. deaths = 436)		Breast Cancer Mortality (No. deaths = 317)	
	Baseline	**Decline**	**Baseline**	**Decline**
Stage of breast cancer at diagnosis*				
Local, N=523	*No. of deaths = 274*		*No. of deaths = 93*	
Functional limitations (continuous)	1.11 (1.03, 1.19)	1.07 (0.94, 1.23)	1.04 (0.92, 1.17)	1.16 (0.97, 1.38)
Functional limitations (≥1 vs. 0)	1.46 (1.05, 2.03)	1.06 (0.75, 1.49)	1.30 (0.76, 2.23)	1.02 (0.59, 1.77)
Regional and ~~Distant~~remote, N=452	*No. of deaths = 162*		*No. of deaths = 224*	
Functional limitations (continuous)	1.03 (0.94, 1.14)	1.19 (1.00, 1.43)	1.02 (0.94, 1.10)	1.08 (0.92, 1.26)
Functional limitations (≥1 vs. 0)	1.58 (0.90, 2.75)	1.61 (1.03, 2.52)	0.66 (0.47, 0.93)	1.19 (0.82, 1.73)
Body mass index at baseline, (kg/m^2)†				
<25, N=454	*No. of deaths = 210*		*No. of deaths = 128*	
Functional limitations (continuous)	1.11 (1.01, 1.22)	1.12 (0.94, 1.32)	1.01 (0.90, 1.14)	1.13 (0.94, 1.36)
Functional limitations (≥1 vs. 0)	1.80 (1.14, 2.84)	1.45 (0.93, 2.27)	0.74 (0.46, 1.18)	1.00 (0.57, 1.73)
25-30, N=323	*No. of deaths = 148*		*No. of deaths = 109*	
Functional limitations (continuous)	1.07 (1.02, 1.13)	1.10 (1.00, 1.21)	0.99 (0.93, 1.06)	1.17 (1.05, 1.31)
Functional limitations (≥1 vs. 0)	1.48 (1.13, 1.94)	1.24 (0.95, 1.60)	0.71 (0.54, 0.95)	1.28 (0.94, 1.73)
>30, N=198	*No. of deaths = 78*		*No. of deaths = 80*	
Functional limitations (continuous)	0.78 (0.60, 1.02)	1.09 (0.68, 1.76)	1.08 (0.92, 1.27)	1.48 (1.09, 2.02)
Functional limitations (≥1 vs. 0)	0.62 (0.18, 2.12)	2.15 (0.70, 6.60)	1.50 (0.61, 3.66)	3.05 (1.32, 7.03)

*Models were stratified by age at breast cancer diagnosis and additionally adjusted for race, comorbidity, breast cancer treatment, body mass index, financial adequacy, education, smoking, positive lymph node involvement, tumor size at diagnosis, and period of study entry.

†Models were stratified by age at breast cancer diagnosis and additionally adjusted for race, comorbidity, breast cancer stage, treatment, financial adequacy, education, smoking, positive lymph node involvement, tumor size at diagnosis, and period of study entry.

Appendix: P-values for the log-rank tests comparing the survival distributions in figures 2a and 2b, by comparison group

Comparison Groups	Other Cause Survival (Figure 2a)	Breast Cancer Survival (Figure 2b)
African-American women with ≥1 functional limitations vs. African-American women without functional limitations	<.0001	0.50
African-American women with ≥1 functional limitations vs. white women with ≥1 functional limitations	0.06	0.05
African-American women without functional limitations vs. white women without functional limitations	0.15	0.20
African-American women without functional limitations vs. white women with ≥1 functional limitations	0.84	0.33
White women with ≥1 functional limitations vs. white women without functional limitations	<.0001	0.50