Title

Mechanisms of association between physical functioning and breast cancer mortality: evidence from the Women's Healthy Eating and Living Study

Journal

Journal of Cancer Survivorship, 8(3)

ISSN

1932-2259

Authors

Marinac, Catherine
Patterson, Ruth E
Villasenor, Adriana
et al.

Publication Date

2014-09-01

DOI

10.1007/s11764-013-0334-2

Peer reviewed

J Cancer Surviv
DOI 10.1007/s11764-013-0334-2

Mechanisms of association between physical functioning and breast cancer mortality: evidence from the Women's Healthy Eating and Living Study

Catherine Marinac · Ruth E. Patterson · Adriana Villasenor · Shirley W. Flatt · John P. Pierce

Received: 15 July 2013 / Accepted: 4 December 2013

Abstract
Purpose Low physical functioning among breast cancer survivors appears to reduce survival, although the mechanisms underlying these associations are not clear. We examined inflammation as a possible biological mediator of association between low physical functioning and mortality after breast cancer.
Methods Analysis included 2,892 participants from the Women's Healthy Eating and Living Study. All measures were collected at study baseline. Physical function was assessed by the Short Form 36 (SF-36) Health Survey Physical Function subscale. Low physical function was defined as the bottom tertile of the subscale score. Inflammation was measured as serum concentration of C-reactive protein (CRP). Cox proportional hazards modeled the associations of low physical function and the putative mediator (i.e., CRP) with all-cause and breast cancer-specific mortality.
Results There were 293 deaths during study follow up, with 243 due to breast cancer. Low physical functioning was associated with a 50 % higher risk of all-cause mortality (HR, 1.49; 95 % CI, 1.2–1.9) and a 40 % higher risk of breast cancer-specific mortality (HR, 1.39; 95 % CI, 1.1–1.8), after adjustment for covariates. The addition of CRP did not markedly change the all-cause mortality hazard ratio attributed to low physical functioning. However, the addition of CRP modestly attenuated the breast cancer-specific mortality hazard ratio such that it was no longer statistically significant.
Conclusions Interventions to improve physical functioning may prevent early morbidity and mortality among breast cancer survivors.
Implications for Cancer Survivors Functional status measure may be a valuable indicator of long-term health outcomes among breast cancer survivors.

Keywords Physical functioning · Obesity · Physical activity · Inflammation · Breast cancer

Introduction

Breast cancer is the most common form of cancer and a leading cause of death among women worldwide. In 2012, an estimated 226,870 women in the USA were diagnosed with breast cancer, and 39,510 died from the disease [1]. Although incidence rates have remained unchanged since 2003, significant progress has been made in the detection and treatment of breast cancer. Concomitantly, a steady increase in the number of women surviving the disease has been observed [2], and more than 2.7 million are alive today with a history of breast cancer. This number is expected to increase to 3.4 million by 2015 [3]. Nonetheless, breast cancer survivors are susceptible to a number of adverse events, such as secondary tumors, cardiovascular disease, diabetes, diminished health-related quality of life, and death [2, 4, 5]. Thus, understanding factors that influence health outcomes for breast cancer survivors is a research priority.

C. Marinac · R. E. Patterson · A. Villasenor · S. W. Flatt · J. P. Pierce
Moores UCSD Cancer Center, University of California, San Diego, La Jolla, CA, USA

C. Marinac
Graduate School of Public Health, San Diego State University, San Diego, CA, USA

R. E. Patterson · A. Villasenor · J. P. Pierce
Department of Family & Preventive Medicine, University of California, San Diego, La Jolla, CA, USA

R. E. Patterson (✉)
Department of Family and Preventive Medicine, Moores UCSD Cancer Center, University of California, San Diego, La Jolla, CA 92093-0824, USA
e-mail: repatterson@ucsd.edu

Published online: 26 February 2014

Functional status measures, such as the ability to complete everyday lifestyle activities, may be an important indicator of short and long-term health outcomes. An estimated 39 % of early-stage breast cancer survivors are limited in their physical functioning abilities [6]. These limitations are linked to immediate health consequences such as poor treatment tolerance, psychological symptoms, disability, falls, and fractures [4, 7, 8]. Breast cancer survivors are susceptible to physical functioning-related problems and often experience treatment-related declines in their physical functioning capabilities within the 1-year period following their cancer diagnosis [9]. Further, physical functioning-related problems may persist even after treatment has been completed [10]. A population-based study of 387 breast cancer survivors documented significant reductions in physical functioning at each follow-up assessment throughout the 10-year study period [11].

Limited physical functioning may also be an indicator of breast cancer survival. In the Life After Cancer Epidemiology (LACE) cohort of 2,202 women with breast cancer, a 40 % higher death rate was reported among women with one or more functional limitations, compared to women with no limitations [6]. In a separate cohort of 689 early-stage breast cancer survivors over age 65, Sehl et al., (2013) found that a change in physical functioning in the first 2 years following breast cancer diagnosis predicted 10-year survival [12]. Specifically, a 23-point decline in Short Form-36 physical functioning subscale score was statistically significantly associated with a 35 % decrease in 10-year survival (a 10-point difference is considered statistically significant).

The mechanisms through which low physical functioning (or change in physical functioning) reduces breast cancer survival may involve compensatory lifestyle adaptations such as increased adiposity (i.e., BMI), physical inactivity, as well as biological responses such as elevated secretion of proinflammatory cytokines and chemokines. In the LACE study, limited physical functioning was strongly associated with overweight and obesity ($p<0.001$) [6]. In the Reach out to Enhance Wellness study of 641 older, sedentary breast cancer survivors, a 2-year multicomponent diet and physical activity intervention resulted in significant improvements in physical activity, BMI, and functional limitations ($p<0.001$) [13]. Other strength- and aerobic-based exercise interventions have found improvements in physical functioning, even independent of weight loss [14]. Furthermore, strong relationships between physical functioning and inflammation have been observed among diverse groups of healthy and diseased populations. A study of 2,287 adult men and women over 60 years from the National Health and Nutrition Examination Survey (NHANES 1999–2004) found 1 mg/l unit increases in C-reactive protein (CRP) concentrations to be associated with a 1 % increase in the prevalence ratios of physical functioning problems (PR, 1.01; 95 % CI, 1.00–1.01; $p=0.001$) [15]. Finally, a cross-sectional study of 542 older men and women with various diseases observed significant inverse associations between objectively measured physical functioning and the inflammatory markers CRP and interleukin-6 (both $p<0.01$) [16].

The objective of this study is to examine mechanisms through which low physical functioning contributes to all-cause mortality among breast cancer survivors. As depicted in Fig. 1, we explored the hypothesis that interrelationships among physical functioning, BMI, physical activity, and inflammation influence mortality after breast cancer. Specifically, low physical functional status may result in increased body weight and low levels of physical activity, both of which contribution to chronic inflammation, which is postulated to increase the risk of mortality among breast cancer survivors. We prospectively examined associations between baseline physical functioning (measured by the SF-36) and clinical outcomes among participants in the Women's Healthy Eating and Living (WHEL) Study [17]. We explored inflammation (as assessed by C-reactive protein) as a possible biological mediator of the association of poor physical functioning and mortality using a causal steps approach as outlined by Baron and Kenny [18].

Methods

Study design and sample This study used data from the Women's Healthy Eating and Living (WHEL) Study, which was a multisite clinical trial to test whether a diet rich in vegetables, fruit, and fiber and low in fat reduced the risk of breast cancer recurrence among 3,088 breast cancer survivors. Details of the WHEL Study eligibility criteria, data collection processes and procedures, and outcome ascertainment have been described elsewhere [17, 19]. To summarize, the WHEL study enrolled 3,088 women at seven study sites between 1995 and 2000. Women were diagnosed with primary operable invasive stage I (≥1 cm), II, or IIIA breast carcinoma within 4 years of enrollment; were ages 18–70 years at diagnosis; had no current or planned chemotherapy; presented no evidence of recurrent disease or new breast cancer since completion of initial treatment; and had no other diagnosed cancers within the previous 10 years. Study participants completed a series of study questionnaires at their baseline clinic visit (baseline assessment period). Height, weight, and a fasting blood specimen were also collected at the baseline clinic visit, prior to randomization. The Institutional Review Boards at the seven study sites approved all study procedures.

As reported in 2007, the dietary intervention of the WHEL study did not reduce additional breast cancer events or mortality during the study's 7.3-year follow-up period. Given this null result [19], we treated WHEL participants as a single cohort for this analysis.

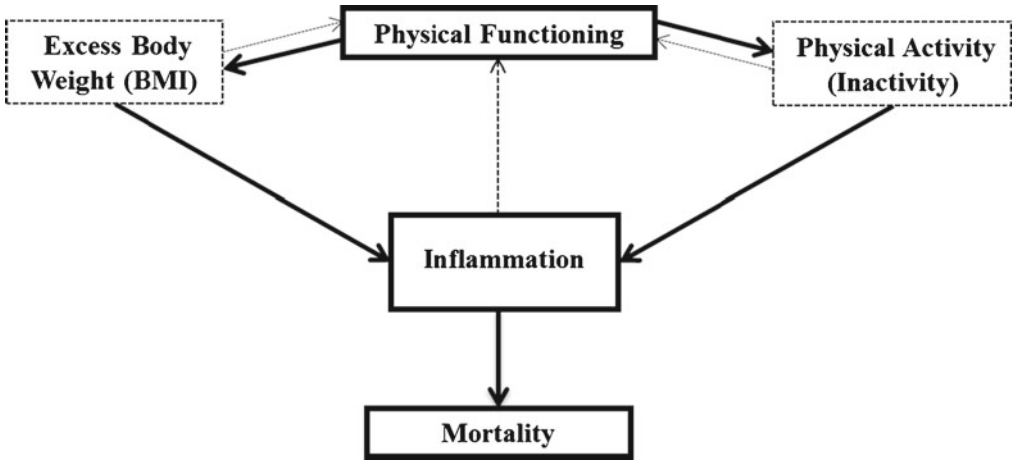

Fig. 1 Simplified model illustrating the hypothesized relationships between low physical functioning, inflammation, lifestyle factors, and mortality after breast cancer. *Solid arrows* primary hypothesized pathways through which physical functioning influences mortality (examined in this paper). *Dashed arrows* other empirically supported (inverse) relationships among study variables

Assessment of physical function At the baseline assessment period, physical function was assessed using the 10-item physical function subscale (PF-10) of the Medical Outcomes Study Short Form-36 (SF-36) [20]. This physical function subscale provides an assessment of the impact of health on the performance of activities ranging from basic self-care to vigorous physical activity. The subscale has been widely used for healthy and diseased populations and has suitable construct validity and sensitivity to change [20]. Physical function subscale scores range from 0 to 100, with higher scores indicating better physical function. A proportion of our sample received subscale scores of 100 and thus was right censored. To account for this right censoring, we categorized physical functioning scores into tertiles. Women in the bottom tertile of physical function scores were considered the "low physical function" group. Women in the upper two tertiles were considered the "adequate physical function" group.

Other assessments Height and weight were measured at baseline clinic visits using standard protocols. Body mass index (BMI, in kilogram per square minute) was calculated and grouped according to the following categories: underweight (<18.5 kg/m^2), normal weight (18.5–24.99 kg/m^2), overweight (25–29.99 kg/m^2), obese I (30–34.99 kg/m^2), and obese II (≥35 kg/m^2).

Physical activity levels were ascertained at baseline by a questionnaire adapted from the Women's Health Initiative [21]. This questionnaire assessed the frequency, duration, and speed of walking outside the home, as well as frequency and duration of participating in intensity levels of exercise (e.g., mild, moderate, and strenuous). The WHEL physical activity measures have been validated against physical activity recalls and objective accelerometry-based assessments [22]. We converted physical activity into units of metabolic equivalent (MET) hours per week and categorized into quintiles of distribution, as was previously published [23, 24].

Fasting blood specimens were collected at baseline clinic visit by venipuncture using a standardized protocol that included protection of samples from light. Aliquots of serum samples were stored at −80C. Serum concentrations of high-sensitivity CRP were assayed at the University of Vermont Laboratory for Clinical Biochemistry Research using a single serum cryovial from each participant. Determination of serum CRP concentration was based on an electrochemiluminescence singleplex system (Meso Scale Discovery, Gaithersburg, MD, USA). The lower detection limits for CRP was 0.0001 mg/L and the inter-assay coefficients of variation were between 7 and 12 %. We use the Centers for Disease Control and Prevention and the American Heart Association cut-points for CRP to present descriptive trends of CRP by physical function tertiles. CRP was analyzed as a continuous variable in Cox proportional hazards regression models based on model fit parameters. Specifically, treatment of CRP as a continuous variable in regression models had a smaller Akaike information criterion than when CRP was categorized. A logarithmic transformation normalized the distribution of CRP concentrations for use in regression analyses.

Outcome ascertainment The outcomes of interest include all-cause mortality and breast cancer-specific mortality. Death from all cause was assessed as the time from cancer diagnosis to death from any cause, or the end of the follow-up period.

Breast cancer mortality was the time from cancer diagnosis to death from breast cancer, or the end of the follow-up period. Outcome information was acquired through active surveillance (semi-annual telephone calls) and periodic review of the Social Security Death Index to confirm death of women who could not be reached. Cause of death was obtained from a death certificate for each decedent and confirmed by the WHEL Clinical Director.

Statistical analyses Cohort descriptors (age, education, and breast cancer characteristics) and lifestyle variables are presented by tertiles of physical functioning scores. Spearman's rank-order correlations were computed for the interrelationships among physical functional status, physical activity MET hours/week, BMI, and CRP. A causal steps mediation analysis was conducted to explore the role of CRP as a potential mediator of the relationship between low physical functioning and health outcomes [18]. Univariate logistic regression modeled odds ratios and confidence intervals for associations of predictor variables with low physical functioning. Delayed-entry Cox proportional hazards were used to model the relative risk of low physical functioning (versus adequate functioning) on all-cause mortality and breast cancer-specific mortality after adjustment for age, cancer stage and grade, education, race, and time between diagnosis and study entry. Models for breast cancer death censored deaths from other causes. Mediation was assessed by comparing the hazard ratios associated with physical functioning in the model described above (base model) to the hazard ratios associated with physical functioning in models containing the putative mediator (CRP). Mediation was indicated by physical functioning hazard ratios moving substantially toward the null when CRP was included. Hosmer–Lemeshow goodness-of-fit statistics were computed for all logistic regression models. Kolmogorov-type Supremum tests and Kaplan–Meier curves assessed the proportionality assumption for all Cox models. All logistic regression models satisfied the Hosmer–Lemeshow goodness-of-fit statistic, and all Cox proportional hazard models fulfilled the proportionality assumption. Statistical tests were two-sided, and analyses were conducted in SAS version 9.3 (Cary, NC, USA).

Results

The final analytic sample was composed of all women who completed the quality of life assessment and had an assayable blood specimen collected at baseline (n =2,892). The mean (SD) baseline age of participants was 52.8 (8.9)years and BMI was 27.3 (6.1)kg/m^2. Roughly half of the women met the physical activity recommendations of 150 min of moderate–vigorous physical activity per week. With regard to the tumor at characteristics at diagnosis, 45.4 % were stage II and 15.9 % stage III; approximately 74.3 % of the original tumors were estrogen-receptor positive. At the end of the 7.3-year follow-up period, there were 293 (10.0 %) deaths from all causes. Approximately 83 % of deaths (n =243) were due to breast cancer.

Compared to women in the bottom tertile of physical functioning scores (lower physical functioning), women in the upper tertiles were younger, received more years of formal education, and had tumors of lower stage and grade (all p <0.05; Table 1). Women in the upper tertiles of physical functioning scores were less overweight or obese and more physically active compared to women in the lowest tertile of physical functioning scores (p <0.001). Further, women in the upper tertiles of physical functioning scores had lower CRP concentrations, compared to women in the lowest tertile of physical functioning scores (p <0.001). Physical functioning was not significantly related to menopausal status or breast cancer treatment (data not shown).

As shown in Table 2, lifestyle variables and CRP were modestly and statistically significantly correlated with physical functioning (all p <0.001). BMI and CRP were inversely correlated with physical functioning, whereas physical activity was directly correlated. Both lifestyle variables were significantly correlated with CRP. The strongest association was between BMI and CRP (r_s =0.6).

Logistic regression analyses yielded statistically significant associations of low physical functioning (dichotomous outcome) with CRP concentrations, BMI, and physical activity (all p <0.001; Table 3). Specifically, women with high CRP concentrations were threefold more likely to have low physical functioning. Obese women were five times more likely to have low physical functioning compared to normal-weight women. Finally, women who did not meet physical activity recommendations were three times more likely to have low physical functioning.

Multivariable-adjusted associations between low physical functioning (dichotomous variable) and breast cancer outcomes were calculated using a delayed-entry survival model (Table 4). Low physical functioning scores at baseline were associated with risk of death from all-cause, and death due to breast cancer. Specifically, women in the low physical functioning category had a 50 % higher risk of all-cause mortality relative to those who were in adequate physical functioning (HR, 1.49; 95 % CI, 1.2–1.9), adjusted for age, stage, grade, race, and education. Similarly, women in the low physical functioning category had a 40 % higher risk of breast cancer-specific mortality (HR, 1.39; 95 % CI, 1.1–1.8; base models).

In model 2, the addition of log-transformed CRP to the all-cause mortality base model modestly attenuated the all-cause mortality hazard ratio associated with low physical functioning, although it remained statistically significant (HR, 1.36; 95 % CI, 1.1–1.74). However, the addition of log-transformed CRP to the breast cancer mortality base model moved the

Table 1 Women's Healthy Eating and Living (WHEL) study participant characteristics by tertiles of physical functioning scores

Baseline characteristics	Tertiles of physical functioning (low to high)			
	1 *N*=929	2 *N*=1249	3 *N*=714	*p* value
Physical function score; median (IQR)	70.0 (20.0)	90.0 (5.0)	100 (0)	<0.001
Age, years; mean (SD)	54.5 (9.0)	52.8 (8.9)	50.5 (8.6)	<0.001
Education, has college degree %	45.1	56.0	62.1	<0.001
Race, white %	82.6	87.3	85.3	0.006
Grade 3 %	38.7	34.5	34.5	0.08
Stage 3 %	18.2	16.0	12.4	0.005
C-reactive protein %				<0.001
<1 mg/L		20.2	35.9	46.2
1–3 mg/L	29.8	34.3	30.7	
≥3 mg/L	50.0	29.9	23.1	
BMI (kg/m^2) %				<0.001
<25	25.7	47.5	57.4	
25–29.9	30.4	32.0	29.6	
≥30	43.9	20.5	13.1	
Not meeting physical activity guidelines[a] %	65.4	44.7	30.5	<0.001

[a] 2008 physical activity guidelines for averaging ≥150 min of moderate–vigorous physical activity per week

hazard ratios associated with low physical functioning towards the null (HR, 1.28; 95 % CI, 0.98–1.67).

Discussion

In this cohort of early-stage breast cancer survivors, low self-rated physical functioning was significantly associated with a 50 % greater risk of all-cause mortality, and a 40 % greater risk of breast cancer-specific mortality. It is notable that low physical functioning, BMI, physical activity, and CRP were all significantly interrelated; and the relationship between low physical functioning and breast cancer-specific mortality was attenuated in models adjusted for CRP. These results suggest that inflammation could be a central biological mechanism through which low physical function contributes to early death from breast cancer.

Our results are similar to the study of self-reported physical functional ability and all-cause mortality among 2,002 breast cancer survivors in the LACE study [6]. The authors of that study found that women with low physical functioning had a 40 % greater risk of all-cause mortality, but found no association between low physical functioning and breast cancer-specific mortality. In contrast, our data suggest that low physical functioning was associated with breast cancer-specific mortality. This discrepancy between the LACE and WHEL findings may be due differences in participant and tumor characteristics. Specifically, WHEL study participants were younger at diagnosis, had more aggressive tumor patterns, and a lower proportion of hormone positive original tumors [17, 25]; all of which are established risk factors for recurrence and breast-cancer-specific mortality [26, 27]. The discrepancy between LACE and WHEL findings may also be due to the fact that the LACE cohort was composed of older women who were more likely to have comorbidities linked to early mortality [28]. Accordingly, a greater proportion of women in the LACE cohort died from causes other than breast cancer (i.e., comorbidities), compared to women in the WHEL cohort.

Table 2 Spearman's rank-order correlation matrix of physical functioning, lifestyle variables, and CRP concentrations from Women's Healthy Eating and Living (WHEL) study participants

	Physical function	Physical activity	BMI (kg/m^2)	Ln (CRP)
Physical function	1.00	0.34*	−0.35*	−0.29*
Physical activity		1.00	−0.29*	−0.29*
BMI (kg/m^2)			1.00	0.59*
Ln (CRP)				1.00

* p <0.001

Table 3 Separate logistic regression models examining the odds of low physical functioning by Women's Healthy Eating and Living (WHEL) study participant characteristics

Baseline characteristics	OR (95%CI)	*p* value
Age, years	1.03 (1.02–1.04)	<0.001
Education (has college degree vs. not)	0.59 (0.51–0.69)	<0.001
Race (white vs. other)	0.72 (0.58–0.89)	<0.001
Grade (3 vs. other)	1.20 (1.03–1.41)	0.02
Stage (3 vs. other)	1.29 (1.05–1.58)	0.02
C-reactive protein		
<1 mg/L	Referent	
1–3 mg/L	1.64 (1.34–2.02)	<0.001
≥3 mg/L	3.31 (2.73–4.02)	<0.001
Body mass index (kg/m^2)		
<25	Referent	
25–29.9	1.91 (1.60–2.36)	<0.001
≥30	4.91 (4.03–5.98)	<0.001
Not meeting physical activity guidelines[a]	2.89 (2.47–3.40)	<0.001

Bottom tertile of physical functioning scores (tertile 1) as assessed by the Short Form 36 (SF-36) Health Survey Physical Function Subscale

[a] Meets 2008 physical activity guidelines for averaging ≥10 metabolic equivalent (MET) hours per of physical activity

Our results are also consistent with evidence linking CRP to poor prognosis in several types of solid cancers, including breast cancer. A study of 2,910 breast cancer survivors found that elevated levels of CRP were associated with all-cause and breast cancer mortality [29]. Inflammation may also contribute to the development of other co-morbid conditions, such as cardiovascular disease [30], Alzheimer's disease [31], and other cancers [32]. Thus, our finding that inflammation may play an intermediate role in the relationship between low physical functioning and breast cancer mortality, suggests that interventions to improve physical functioning might prevent morbidity as well as mortality.

Table 4 Physical functioning and health outcomes: Associations of Physical Functioning with All-Cause Mortality and Breast Cancer-Specific Mortality. Models are delayed-entry Cox proportional hazard models, adjusted for the time interval between breast cancer diagnosis and physical functioning assessment

	All-cause mortality HR (95 % CI) Events (*n* = 293)	Breast cancer mortality HR (95%CI) Events (*n* = 243)
Model 1 (base model)		
Low physical functioning[a]	1.49 (1.17–1.89)	1.39 (1.07–1.80)
Adequate physical functioning	Referent	Referent
Model 2		
Low physical functioning	1.36 (1.07–1.74)	1.28 (0.98–1.67)
Adequate physical functioning	Referent	Referent
Ln (C-reactive protein)	1.17 (1.06–1.29)	1.16 (1.04–1.28)

All models adjusted for age, stage, grade, education, and race

[a] Bottom tertile of physical functioning scores (tertile 1)

The finding that lifestyle factors such as physical inactivity and obesity are significantly associated with both low physical functioning and CRP may indicate that lifestyle and physical functioning may work through effects on obesity and physical activity to increase inflammation (which may have subsequent effects on mortality). Specifically, physical activity and/or weight loss may produce beneficial effects in breast cancer survivors by modulating circulating biomarkers of inflammation; and these effects of lifestyle on biomarkers of inflammation are both biologically plausible and supported by epidemiologic evidence. For example, a randomized controlled trial conducted by Nakajima and colleagues demonstrated that a 6-month high-intensity walking program (26 min of interval walking training, a minimum of 2 days per week) can lead to an increase in methylation of a gene known to secrete proinflammatory cytokines [33]. Consistent with this biological support, epidemiological studies in breast cancer populations have noted evidence of a protective effect of physical activity on inflammation. An analysis of data from 1,183 women in the Health, Eating, Activity, and Lifestyle (HEAL) cohort of breast cancer survivors found that higher levels of physical activity were associated with lower concentrations of C-reactive protein [34]. With respect to the observed associations between obesity and inflammation, there is mechanistic evidence that tumor necrosis alpha (TNF-α) production is increased in obesity, which can stimulate the production of CRP [35–37]. Statistically significant correlations between CRP and BMI have also noted in breast cancer cohorts [34].

Our analysis has several limitations. CRP and physical functioning measures were ascertained from blood specimens and surveys collected at the same time point. Therefore, we were not able to eliminate the possibility of reverse causality for the association of low physical functioning and higher CRP concentrations. It is possible that the relationship between low physical functioning and inflammation is bidirectional. Data from laboratory and animal studies suggest that high levels of circulating inflammatory biomarkers may result in skeletal muscle catabolism. In rats, direct infusion of IL-6 results in muscle atrophy and a loss of myofibrillar protein [38]. However, human data suggests the effect of inflammation on muscle breakdown may be minimal. The association between physical functioning and inflammation appears to remain strong, even after adjusting for dual energy X-ray absorptiometry measured lean body mass [16]. The same possibility of reverse causality exists for the relationship between low physical function and lifestyle factors such as physical activity and obesity. We acknowledge that unhealthy lifestyles such as physical inactivity and obesity may

contribute to low physical functioning; however, it is equally probable that low physical functioning exacerbates characteristics of an unhealthy lifestyle (the direction explored in this analysis). For example, women with low physical functioning due to joint pain (a common symptom of physical functional status) may become less physically active, more susceptible to weight gain, and consequently at an elevated risk of early mortality. No study, to our knowledge has examined the temporal relationships of physical functioning and lifestyle factors such as physical activity and obesity.

Additional limitations include the fact that, although we adjusted for potential confounders, we cannot exclude residual confounding by unmeasured factors (such as anti-inflammatory medication use) or by imperfectly or incompletely measured confounders. We also used a self-report measure of physical activity; however, this measure has been validated by seven physical activity recalls and 7-day accelerometers [22]. Further, we used a single, nonspecific biomarker to represent inflammatory processes. We also acknowledge that inflammation processes involve numerous molecules that interact in complex ways. However, CRP is thought to be a useful indicator of multiple inflammatory processes. CRP has a strong covariance with other biomarkers of inflammation and hepatic synthesis of CRP is augmented by proinflammatory cytokines, such as IL-6, IL-1beta, and TNF-α [31, 39].

WHEL study participants were healthier than the general population of breast cancer survivors. Over 53 % of WHEL women met physical activity recommendations at study baseline (compared to roughly 37 % in the general population of breast cancer survivors) [40]. The fact that lifestyle was a mediator of the relationship between physical functioning and mortality in this healthier sample of women suggests that the observed relationships will be even stronger in less healthy populations. However, this finding needs to be replicated in more general populations of breast cancer survivors.

Strengths of this study include use of a valid and reliable measure of physical functioning, and an objective biomarker of inflammation. We also used verified patient data on tumor characteristics and deaths during the study follow-up period and we had detailed information on potential confounding characteristics including demographic and lifestyle variables. Further, the results of this study are strengthened by the fact that our study used data from a geographically diverse population of women participating in a multisite trial.

Findings from this study contribute to the evidence that functional status measures are important indicators of long-term prognosis following breast cancer treatment. To our knowledge, this is the first study to explore mechanisms of association between low physical functioning and early mortality among breast cancer survivors. Our findings offer the strongest evidence to date that inflammation may be a biological mechanism through which low physical functioning impacts breast cancer mortality. Much work still needs to be done in both elucidating and intervening in the relation of inflammation, and physical functional status with mortality in breast cancer survivors. Future interventions aimed at improving physical functioning and measuring inflammatory biomarkers at different time points are needed. These studies could clarify the causal associations between physical functional status and inflammation. If confirmed, self-reported information on physical functional status may be a valuable indicator of future morbidity and mortality. These findings underscore the need for functional status measures, which can identify high-risk population subgroups, to be incorporated into survivorship care plans.

Acknowledgments Ms. Marinac is a recipient of a Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Training Grant (T32), awarded to San Diego State University by the National Institute of General Medical Sciences (5 T32 GM084896). The Women's Healthy Eating and Living (WHEL) Study was initiated with the support of the Walton Family Foundation and continued with funding from National Cancer Institute Grant No. CA 69375 and Komen grant no. 100988. Some of the data were collected from General Clinical Research Centers, National Institutes of Health grants no.M01-RR00070, M01-RR00079, and M01-RR00827.

Conflict of interest The authors declare that they have no financial or non-financial conflict of interest.

References

1. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Altekruse SF, et al. SEER cancer statistics review, 1975–2009; based on November 2011 SEER data submission, posted to the SEER Website. 2011. Bethesda, MD: National Cancer Institute, 2012. http://seer.cancer.gov/csr/1975_2009_pops09/. Accessed 8 Feb 2013.
2. Yabroff KR, Lawrence WF, Clauser S, Davis WW, Brown ML. Burden of illness in cancer survivors: findings from a population-based national sample. J Natl Cancer Inst. 2004;96:1322–30.
3. De Angelis R, Tavilla A, Verdecchia A, Scoppa S, Hachey M, Feuer EJ, et al. Breast cancer survivors in the United States: geographic variability and time trends, 2005–2015. Cancer. 2009;115:1954–66.
4. Bardwell WA, Major JM, Rock CL, Newman VA, Thomson CA, Chilton JA, et al. Health-related quality of life in women previously treated for early-stage breast cancer. Psychooncology. 2004;13:595–604.
5. Patnaik JL, Byers T, Diguiseppi C, Denberg TD, Dabelea D. The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst. 2011;103:1101–11.
6. Braithwaite D, Satariano WA, Sternfeld B, Hiatt RA, Ganz PA, Kerlikowske K, et al. Long-term prognostic role of functional limitations among women with breast cancer. J Natl Cancer Inst. 2010;102:1468–77.
7. Clough-Gorr KM, Stuck AE, Thwin SS, Silliman RA. Older breast cancer survivors: geriatric assessment domains are associated with poor tolerance of treatment adverse effects and predict mortality over 7 years of follow-up. J Clin Oncol. 2010;28:380–6.
8. Keeler E, Guralnik JM, Tian H, Wallace RB, Reuben DB. The impact of functional status on life expectancy in older persons. J Gerontol A Biol Sci Med Sci. 2010;65:727–33.
9. Ganz PA, Kwan L, Stanton AL, Krupnick JL, Rowland JH, Meyerowitz BE, et al. Quality of life at the end of primary treatment

of breast cancer: first results from the moving beyond cancer randomized trial. J Natl Cancer Inst. 2004;96:376–87.
10. Ganz PA, Kwan L, Stanton AL, Bower JE, Belin TR. Physical and psychosocial recovery in the year after primary treatment of breast cancer. J Clin Oncol. 2011;29:1101–9.
11. Koch L, Jansen L, Herrmann A, Stegmaier C, Holleczek B, Singer S, et al. Quality of life in long-term breast cancer survivors—a 10-year longitudinal population-based study. Acta Oncol. 2013;6:1119–28.
12. Sehl M, Lu X, Silliman R, Ganz PA. Decline in physical functioning in first 2 years after breast cancer diagnosis predicts 10-year survival in older women. J Cancer Surviv. 2013;7:20–31.
13. Demark-Wahnefried W, Morey MC, Sloane R, Snyder DC, Miller PE, Hartman TJ, et al. Reach out to enhance wellness home-based diet-exercise intervention promotes reproducible and sustainable long-term improvements in health behaviors, body weight, and physical functioning in older, overweight/obese cancer survivors. J Clin Oncol. 2012;30:2354–61.
14. Winters-Stone KM, Dobek J, Bennett JA, Nail LM, Leo MC, Schwartz A. The effect of resistance training on muscle strength and physical function in older, postmenopausal breast cancer survivors: a randomized controlled trial. J Cancer Surviv. 2012;6:189–99.
15. Levine ME, Crimmins EM. The impact of insulin resistance and inflammation on the association between sarcopenic obesity and physical functioning. Obesity. 2012;20:2101–6.
16. Brinkley TE, Leng X, Miller ME, Kitzman DW, Pahor M, Berry MJ, et al. Chronic inflammation is associated with low physical function in older adults across multiple comorbidities. J Gerontol A Biol Sci Med Sci. 2009;64:455–61.
17. Pierce JP, Faerber S, Wright FA, Rock CL, Newman V, Flatt SW, et al. A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. Control Clin Trials. 2002;23:728–56.
18. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986;51:1173–82.
19. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA. 2007;298:289–98.
20. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Conceptual framework and item selection. Med Care. 1992;30:473–83.
21. McTiernan A, Kooperberg C, White E, Wilcox S, Coates R, Adams-Campbell LL, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. JAMA. 2003;290:1331–6.
22. Johnson-Kozlow M, Rock CL, Gilpin EA, Hollenbach KA, Pierce JP. Validation of the WHI brief physical activity questionnaire among women diagnosed with breast cancer. Am J Health Behav. 2007;31:193–202.
23. Hong S, Bardwell WA, Natarajan L, Flatt SW, Rock CL, Newman VA, et al. Correlates of physical activity level in breast cancer survivors participating in the Women's Healthy Eating and Living (WHEL) Study. Breast Cancer Res Treat. 2007;101:225–32.
24. Bertram LAC, Stefanick ML, Saquib N, Natarajan L, Patterson RE, Bardwell W, et al. Physical activity, additional breast cancer events, and mortality among early-stage breast cancer survivors: findings from the WHEL Study. Cancer Causes Control. 2011;22:427–35.
25. Caan B, Sternfeld B, Gunderson E, Coates A, Quesenberry C, Slattery ML. Life After Cancer Epidemiology (LACE) Study: a cohort of early stage breast cancer survivors (United States). Cancer Cause Control. 2005;16:545–56.
26. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res. 2007;9:R6.
27. Cianfrocca M, Goldstein LJ. Prognostic and predictive factors in early-stage breast cancer. Oncologist. 2004;9:606–16.
28. Center for Disease Control. Healthy aging data portfolio—state of aging and health in America Report. http://apps.nccd.cdc.gov/SAHA/Default/Default.aspx. Accessed 8 Feb 2013.
29. Allin KH, Nordestgaard BG, Flyger H, Bojesen SE. Elevated pretreatment levels of plasma C-reactive protein are associated with poor prognosis after breast cancer: a cohort study. Breast Cancer Res. 2011;13:R55.
30. Corrado E, Rizzo M, Coppola G, Fattouch K, Novo G, Marturana I, et al. An update on the role of markers of inflammation in atherosclerosis. J Atheroscler Thromb. 2010;17:1–11.
31. Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, et al. Systemic inflammation and disease progression in Alzheimer disease. Neurology. 2009;73:768–74.
32. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol. 2004;287:G7–17.
33. Nakajima K, Takeoka M, Mori M, Hashimoto S, Sakurai A, Nose H, et al. Exercise effects on methylation of ASC gene. Int J Sports Med. 2010;31:671–5.
34. Pierce BL, Neuhouser ML, Wener MH, Bernstein L, Baumgartner RN, Ballard-Barbash R, et al. Correlates of circulating C-reactive protein and serum amyloid A concentrations in breast cancer survivors. Breast Cancer Res Treat. 2009;114:155–67.
35. Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. Front Endocrinol. 2013;4:71.
36. Procaccini C, De Rosa V, Galgani M, Carbone F, La Rocca C, Formisano L, et al. Role of adipokines signaling in the modulation of T cells function. Front Immunol. 2013;4:332.
37. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest. 1995;95:2409–15.
38. Haddad F, Zaldivar F, Cooper DM, Adams GR. IL-6-induced skeletal muscle atrophy. J Appl Physiol. 2005;98:911–7.
39. Heikkilä K, Ebrahim S, Rumley A, Lowe G, Lawlor DA. Associations of circulating C-reactive protein and interleukin-6 with survival in women with and without cancer: findings from the British Women's Heart and Health Study. Cancer Epidemiol Biomarkers Prev. 2007;16:1155–9.
40. Blanchard CM, Courneya KS, Stein K. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. J Clin Oncol. 2008;26:2198–204.