Published in final edited form as:

J Cancer Surviv. 2012 December ; 6(4): 398–406. doi:10.1007/s11764-012-0234-x.

Prevalence and prognostic effect of sarcopenia in breast cancer survivors: the HEAL Study

Adriana Villaseñor,

Cancer Prevention Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, M4-B402, Seattle, WA 98109-1024, USA

School of Public Health, Department of Epidemiology, University of Washington, Seattle, WA, USA

Rachel Ballard-Barbash,

Applied Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD, USA

Kathy Baumgartner,

Department of Epidemiology and Population Health, University of Louisville, Louisville, KY, USA

Richard Baumgartner,

Department of Epidemiology and Population Health, University of Louisville, Louisville, KY, USA

Leslie Bernstein,

Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, City of Hope, Duarte, CA, USA

Anne McTiernan, and

School of Public Health, Department of Epidemiology, University of Washington, Seattle, WA, USA

Epidemiology Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Marian L. Neuhaus

Cancer Prevention Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, M4-B402, Seattle, WA 98109-1024, USA

School of Public Health, Department of Epidemiology, University of Washington, Seattle, WA, USA

Adriana Villaseñor: avillase@fhcrc.org

Abstract

Purpose—This study aimed to determine the prevalence of sarcopenia and examine whether sarcopenia was associated with overall and breast-cancer-specific mortality in a cohort of women diagnosed with breast cancer (stages I–IIIA).

Methods—A total of 471 breast cancer patients from western Washington State and New Mexico who participated in the prospective Health, Eating, Activity, and Lifestyle Study were included in this study. Appendicular lean mass was measured using dual X-ray absorptiometry scans at study

inception, on average, 12 months after diagnosis. Sarcopenia was defined as two standard deviations below the young healthy adult female mean of appendicular lean mass divided by height squared ($<5.45 \text{ kg/m}^2$). Total and breast-cancer-specific mortality data were obtained from Surveillance Epidemiology and End Results registries. Multivariable Cox proportional hazard models assessed the associations between sarcopenia and mortality.

Results—Median follow-up was 9.2 years; 75 women were classified as sarcopenic, and among 92 deaths, 46 were attributed to breast cancer. In multivariable models that included age, race-ethnicity/study site, treatment type, comorbidities, waist circumference, and total body fat percentage, sarcopenia was independently associated with overall mortality (hazard ratio (HR)=2.86; 95 % CI, 1.67– 4.89). Sarcopenic women had increased risk of breast-cancer-specific mortality, although the association was not statistically significant (HR=1.95, 95 % CI, 0.87– 4.35).

Conclusion—Sarcopenia is associated with an increased risk of overall mortality in breast cancer survivors and may be associated with breast-cancer-specific mortality. The development of effective interventions to maintain and/or increase skeletal muscle mass to improve prognosis in breast cancer survivors warrants further study.

Implications for Cancer Survivors—Such interventions may help breast cancer patients live longer.

Keywords

Sarcopenia; Appendicular lean mass; Mortality; Breast cancer survivor

Introduction

Research between body composition and cancer outcomes usually focuses on the prognostic effects of excess body fat [1, 2], yet emerging evidence supports severe depletion of skeletal muscle (sarcopenia) as an important predictor of cancer outcomes [3–7]. Commonly observed in older age groups [7–9], sarcopenia is associated with poor muscle strength, functional impairment, and disability [10–15]. Sarcopenia prevalence estimates range from 5 to 13 % among persons aged 60–70 years and from 11 to 50 % in persons over 80 years of age [9, 10]. Of interest, individuals diagnosed with some forms of cancer may experience a marked and progressive weight loss, primarily of skeletal muscle, resulting in severe depletion of skeletal muscle or sarcopenia [5, 16]. In cancer patients, sarcopenia is associated with treatment failure, chemotherapy toxicity, and a shorter time to tumor progression related to survival [3–5]. Prado et al. reported associations between sarcopenia and poor prognostic outcomes in breast, gastrointestinal, and lung cancers. Compared to patients without sarcopenia, those with sarcopenia had a 2.6-fold greater risk of developing a secondary malignancy (hazard ratio (HR)=2.6; 95 % confidence interval (CI), 1.2–5.6 [3]), greater rates of chemotherapy toxicity ($p=0.036$, Student's test) [17], and shorter time to death (mean difference of 7 months; HR=4.2; 95 % CI, 2.4–7.2) [4].

Obese women (defined as body mass index (BMI) $\geq 30.0 \text{ kg/m}^2$ [18]), have greater rates of morbidity and mortality than non-obese women (i.e., BMI $<30.0 \text{ kg/m}^2$) [1, 2]. Furthermore, research suggests that simultaneous occurrence of excess body fat and sarcopenia exacerbates the risk of developing multiple health-related problems [19–22]. In health-frail populations, such as cancer patients, obese individuals with sarcopenia have greater rates of functional impairment, treatment failure, and treatment toxicity and consequently shorter time to tumor progression than obese patients without sarcopenia [4, 5, 19]. In a cohort of overweight/obese pancreatic cancer patients, Tan et al. [5] reported a strong association between sarcopenia and overall mortality (HR=2.1; 95 % CI, 1.1–3.5). Whether

sarcopenia has an impact on survival that is independent of excess body fat is unknown since evidence linking sarcopenia to cancer prognosis is limited. No previous studies have focused on associations of sarcopenia with breast cancer mortality. Here, we report on the prevalence of sarcopenia, assessed by appendicular lean mass relative to height and the association with overall and breast-cancer-specific mortality in a cohort of women diagnosed with invasive breast cancer (stages I–IIIA). We also examine the influence of individual and breast cancer clinical characteristics on sarcopenic status.

Materials and methods

Study population

The Health, Eating, Activity, and Lifestyle (HEAL) Study is a cohort study of women diagnosed with breast cancer designed to examine physical activity, eating habits, weight patterns, diet, hormones, and other prognostic factors for breast cancer. The methods for this multicenter, multiethnic prospective cohort study have been described elsewhere [23]. In brief, using local Surveillance Epidemiology and End Results (SEER) registries of New Mexico (University of New Mexico, UNM), Los Angeles, CA, USA (University of Southern California), and western Washington (Fred Hutchinson Cancer Research Center, FHCRC), we identified and enrolled 1,183 women, >18 years of age, diagnosed with in situ or stage I–IIIA primary incident breast cancer within 12 months of their diagnoses. Participants completed a self-report questionnaire and an in-person interview at study inception. A subset of participants enrolled at UNM study site ($n=532$) and FHCRC study site ($n=109$) completed a baseline clinical visit, including anthropometric measurements and a whole-body dual-energy X-ray absorptiometry (DXA) scan. There were no additional eligibility criteria for participation in anthropometric measurements. Annual data collected from SEER registries and abstracted medical records were used to follow each participant and determine health related outcomes, and mortality due to breast cancer or other causes. For this investigation, the sample was restricted to 471 women diagnosed with invasive breast cancer, had a baseline DXA scan, and were free from any disease recurrence, new primary, or death up to 9 months following study inception. Written informed consent was obtained from each participant. The study was performed with the approval of the Institutional Review Boards of the participating institutions in accordance with an assurance filed with and approved by the US Department of Health and Human Services.

Body composition measurements

Anthropometric measurements—Using standardized methods, body weight, height, and waist circumference were measured with subjects wearing light indoor clothing or a hospital gown without shoes, at the baseline clinical visit [23, 24]. Trained staff conducted anthropometric measures twice, and the average was used in the analysis (Pearson's correlation coefficients, $r=0.99$) [24]. BMI was calculated as weight in kilograms divided by the square of height in meters.

Fat and lean soft tissue measurements—We used DXA to quantify whole- and regional-body composition, at baseline (New Mexico site: Lunar model DPX; Lunar Radiation Corporation, Madison, WI, USA; Washington site: Hologic QDR 1500, Hologic, Inc., Bedford, MA, USA). The DXA scan provided measures of total body fat tissue (nonbone, muscle-free) and lean soft tissue in kilograms (nonbone, fat-free). Lean soft tissue mass was separated into trunk and appendicular components. Appendicular lean mass was calculated as the sum of lean soft tissue mass in the arms and legs and represents the primary proportion of skeletal muscle mass in the body [9, 25]. Total body fat percentage was calculated as the weight of total body fat tissue divided by total body weight. DXA provides

a highly reproducible and accurate measure for body fat tissue and lean soft tissue mass, and is a validated and accepted method for assessing body composition [25, 26].

Outcome ascertainment

Patients were followed for overall mortality and breast-cancer-specific mortality from the date of initial data collection through December 31, 2007. Deaths were classified using *International Classification of Diseases, 10th Revision* (ICD-10) codes [27]. The time frame for the primary end point of interest, overall mortality, was initiated on the date of initial data collection and ended on the date of death. Nondeceased patients were censored on December 31, 2007. The secondary end point of interest, breast-cancer-specific mortality, was defined using ICD-10 code C50 [27]. In analyses of breast cancer deaths, women dying from other causes were censored on their dates of death; nondeceased patients were censored on December 31, 2007.

Other data

We collected standardized information on demographic characteristics, medical history, physical activity, lifestyle habits, and medication use. Breast cancer stage at diagnosis was obtained from the SEER registry records, and breast cancer treatment data were obtained from participants' medical records and SEER.

Statistical analysis

Our analytic goals were to describe the prevalence of sarcopenia in this cohort of breast cancer survivors and characterize the association of sarcopenia with overall and breast-cancer-specific mortality. An appendicular lean mass index was calculated as appendicular lean mass (kilogram) divided by height (meter) squared [8]. Sarcopenia was defined as two standard deviations (SD) below the mean appendicular lean mass index among young healthy female ($<5.45 \text{ kg/m}^2$) [8, 28] and has been shown to be associated with poor function and increased mortality in older age groups [29, 30]. Differences in participant, treatment, and disease-related characteristics, by sarcopenic status, were evaluated using ANOVAs for continuous variable and/or the chisquared statistic for categorical variables. We used the Kaplan–Meier technique to construct survival curves and to calculate 5- and 10-year survival rates [31]. We employed Cox proportional hazards models to estimate the age-adjusted and multivariable HR and 95 % CI for death due to any cause and breast-cancer-specific deaths by sarcopenic status. Age at diagnosis (years) was used as the time metric for all regression analysis. We tested and confirmed nonviolation of the proportionality assumption based on a graphical approach (i.e., log(–log) plots) [32] and the goodness-of-fit test using Schoenfeld residuals [33].

Covariates were examined for inclusion in the final multivariate model based on a list of known or suspected a priori predictors of mortality and sarcopenia from published literature [8–10]. Variables were retained in the final model if they were associated with sarcopenia, associated with mortality in nonsarcopenic survivors and had altered the risk estimate of the model containing sarcopenia plus age by at least 10 %. Because the two study sites had distinct race/ethnic composition, we generated an adjustment variable for race–ethnicity/study site [21]. All models included age, race–ethnicity/study site, waist circumference, body fat percentage, physical activity, breast cancer stage at diagnosis, and treatment type. For overall mortality, we further adjusted for Charlson comorbidity index score [34]. For the breast-cancer-specific mortality models, we further adjusted for tamoxifen use. Interactions were tested by adding a product term for sarcopenic status and each of the following covariates: BMI, menopause, and adjuvant tamoxifen use. Statistical tests were performed using Stata (version 11.1; StataCorp LP, College Station, TX, USA) software. All tests were two-sided, and statistical significance was set at P 0.05.

Results

Among the 471 women included in this analysis, 75 (16 %) were sarcopenic, with 38 % of these women classified as obese (total body fat percentage, 38 %) and 61 % as not obese (<38 %) [21]. The medians, 5th and 95th percentiles, and the ranges are given for age at diagnosis and weight, height, waist circumference, BMI, total body fat percentage, appendicular lean mass, and height-adjusted appendicular lean mass assessed at baseline (Table 1). Sarcopenic women tended to be older at diagnosis, have lower total body weight, smaller waist circumference, and lower BMI compared to nonsarcopenic women. As defined, sarcopenic women had a lower amount and narrower range of appendicular lean mass and, as anticipated, a lower amount and narrow range of total body fat percentage.

Sarcopenia was more common in women who were postmenopausal and were diagnosed with earlier disease stage (Table 2). No differences in prevalence of sarcopenia were found across race–ethnicity/study site, physical activity categories, alcohol use, smoking status, comorbidity index scores, disease treatment, or tamoxifen use.

Between the initial clinic visit and December 31, 2007, 92 deaths occurred of which 46 were due to breast cancer. The median length of follow-up was 9.2 years (ranging between 0.5 and 10.9 years). Results for overall mortality and breast-cancer-specific mortality were similar. Sarcopenia was associated with an increased risk of overall mortality and breast-cancer-specific mortality, although the latter relationship did not reach statistical significance. Figure 1 illustrates the unadjusted overall survival rates by sarcopenic status. The overall 5-year survival rate among sarcopenic women was 85.3 % and among nonsarcopenic women was 92.9 %; comparable 10-year figures were 67.6 and 83.8 %, respectively (log-rank $p=0.0019$, data not shown).

In age-adjusted analysis, sarcopenia was associated with increased risk of any death (Table 3) (HR=1.90; 95 % CI, 1.17–3.08). Next, we examined a series of potential confounders in a sequential manner (models 1–5). Following adjustment for age, race–ethnicity/study site, waist circumference, comorbidity index score, and treatment (model 1), we found sarcopenia to be strongly associated with an increased risk of overall mortality (HR=2.44; 95 % CI, 1.44–4.15). Based on strong evidence that excess body fat has an adverse prognostic effect, we were interested in how the addition of adiposity, modeled as total body fat percentage (model 2) or BMI categories (model 3), would alter the association between sarcopenia and overall mortality [2, 16, 23, 35]. Sarcopenia remained independently predictive of overall mortality regardless of adiposity measure used (total body fat percentage: HR=2.86; 95 % CI, 1.67–4.89; BMI: HR=2.29; 95 % CI, 1.34–3.90). We were also interested in exploring whether additional factors known to affect survival, specifically stage at diagnosis (model 4) and physical activity (model 5), would alter the sarcopenia–survival relationship [36–38]. We found the sarcopenia–mortality relationship did not markedly change following inclusion of either covariate, after adjusting for adiposity (total body fat percentage).

Using a similar approach, we examined factors associated with sarcopenia and breast-cancer-specific mortality. Figure 2 illustrates the unadjusted breast-cancer-specific survival curves by sarcopenic status. The 5-year breast-cancer-specific survival rates were approximately 94.2 % regardless of sarcopenic status, and the 10-year breast-cancer-specific survival rates were 86.5 % in sarcopenic women and 90.5 % in nonsarcopenic women (log-rank $p=0.38$, data not shown). In age-adjusted analysis, sarcopenia was associated with an increased risk of death due to breast cancer (Table 4) (HR= 1.65; 95 % CI, 0.78–3.52); with only nine deaths among the 75 sarcopenic women, the association did not reach statistical significance. With the addition of potential confounding variables (multivariable model)

compared to the age-adjusted model, we did not find a meaningful change to the conclusion that sarcopenia was modestly, but statistically non-significantly associated with breast-cancer-specific mortality (HR=1.95; 95 % CI, 0.87–4.35).

Discussion

In this prospective cohort study of breast cancer survivors, we found a substantial prevalence of sarcopenia (15.9 %), given the relatively young age distribution of this cohort. Notably, sarcopenia was present in breast cancer survivors across the distribution of BMI <30 kg/m². Furthermore, we found that sarcopenia was an independent predictor of poor survival. Sarcopenic women were almost three times more likely to die from any cause (HR=2.86; 95 % CI, 1.67–4.89) and almost two times more likely to die from breast-cancer-specific cause (HR=1.95; 95 % CI, 0.89–4.35), regardless of adiposity, compared to women without sarcopenia. Our observation suggests that depleted skeletal muscle mass may partially explain the variation seen in relation to survival, regardless of adiposity, compared to women without sarcopenia.

To date, four other studies evaluated the adverse effects of depleted skeletal muscle mass in individuals diagnosed with cancer; all reported similar results. In the single study of breast cancer, Prado et al. reported that sarcopenia was independently associated with a higher incidence of treatment induced toxicity and a shorter time to tumor progression among metastatic breast cancer patients (*N*=55), independent of adiposity [3]. In 2007, Prado et al. [17] noted a strong positive association between low skeletal muscle mass and chemotherapy toxicity in colon cancer patients treated with 5-FU and leucovorin (*N*=62). In a separate study, Prado et al. [4] reported that in patients with gastrointestinal cancer or lung cancer (*N*=250), obese patients with sarcopenia had an increased risk of mortality (HR=4.2; 95 % CI, 2.4–7.2) when compared to obese nonsarcopenic patients. Further, Tan et al. [5] reported that sarcopenia was an independent predictor of mortality among overweight/obese pancreatic cancer patients (*N*=111) (HR =2.07; 95 % CI, 1.23–3.50). While the methods of body composition analysis differed between our study (DXA scan) and studies by Prado et al. and Tan et al. (CT scans), both approaches showed that sarcopenia was strongly associated with adverse prognostic factors (treatment induced toxicity and time to tumor progression) and decreased survival.

Several mechanisms have been proposed to explain the potential adverse effect of low relative skeletal muscle mass on breast cancer prognosis [3–5, 17]. First, chemotherapy dosing protocols use body-surface area to estimate the amount of metabolic target tissue [39–41]. Given the heterogeneity in distribution of lean soft tissue and fat tissues across the BMI distribution, the use of body-surface area may result in an overestimation or an underestimation of actual metabolic target tissues [41]. Potential mismatches in chemotherapy dosing may help explain the association of sarcopenia with increased risk of chemotherapeutic toxicity and treatment failure [3, 17]. Second, sarcopenia is associated with functional impairment and muscle weakness [19, 22, 42], which may influence important lifestyle habits such as poor dietary nutrient intake, decreased physical activity, weight gain, and tobacco or alcohol use, which are recognizable risk factors for adverse prognosis of breast cancer.[16, 35, 43–45] Finally, muscle tissue has multiple important functions, such as glucose homeostasis and insulin sensitivity, respiratory integrity, and cardiac output [46]; therefore, a significant reduction of muscle mass may further increase the risk of adverse outcomes in patients with breast cancer.

Research on the effect of depleted skeletal muscle mass on morbidity and mortality has been limited both by the lack of an operational definition, as well as by the challenge of reliably quantifying lean mass in large population studies [47]. Baumgartner was the first to use a

dichotomous method based on two standard deviations below the sex-specific mean of height-adjusted appendicular lean mass in young healthy adults, as measured by DXA [5, 8, 48, 49]. Other approaches have used similar types of cut-points using other measurement tools (e.g., bioelectrical impedance and computed tomography) or used residuals from linear regression models of lean mass given fat mass and height, or fat-mass cut points associated with adverse outcomes in vulnerable populations (e.g., lung cancer patients) [3, 4, 17]. Newman et al. [47] demonstrated variation in prevalence of sarcopenia and impact for prognostic outcomes were dependent on both the quantitative method used and definition of sarcopenia. Thus, a standard approach for both measuring and defining sarcopenia is necessary to accurately describe the extent and impact of sarcopenia. A recent collaborative report recommended that both a combined presence of reduced physical functioning measured as a gait speed $<1 \text{ m/s}^{-1}$ plus reduced muscle mass, using an T score of muscle mass (corrected for either height, body weight or fat mass) two SD or less be used [46]. Further methodological work is needed in this area.

The strengths of our study include a well-characterized cohort with a larger sample size ($N=471$) compared to prior studies examining sarcopenia and cancer outcomes. We used well-annotated tumor-, treatment-, and traditional prognostic-related data and have approximately 11 years of well-documented outcomes based on medical record reviews and annual SEER registry updates. We used DXA scan to assess body composition [42, 50–52]. DXA has a good reported reproducibility, with coefficients of variation (CV%) for total body fat mass of 1–2 %, for total body fat-free and total body lean tissue of 1–2 %, for arm lean soft tissue of 3–4 %, and for leg lean soft tissue of 1–2 % [26, 50].

Limitations included the observational design and therefore causality cannot be inferred. We adjusted our models for clinical and lifestyle-related factors, alcohol intake, physical activity, and smoking status. Residual confounding, however, may still exist. Sarcopenia may be a surrogate variable for the true causal exposures, such as BMI or physical activity, through alternative mechanisms [16, 23]. Furthermore, there is evidence that the sarcopenia–mortality association is more apparent in women with excessive adiposity (BMI $>30 \text{ kg/m}^2$) [3–5]; however, we had no obese women based on BMI with sarcopenia in our cohort. Our observations for sarcopenia did not change when adjusted for total body fat percentage or hours of physical activity, and no significant interactions were observed. Lastly, a limited number of deaths were documented in our cohort as breast-cancer-specific deaths, limiting the statistical power to examine breast-cancer-specific mortality by sarcopenic status. Given extensive published evidence of the positive association between sarcopenia and mortality, our finding for all-cause mortality is unlikely to be due to chance.

Data from this cohort of breast cancer survivors suggest that sarcopenia may be an independent predictor of mortality, regardless of adiposity. Further research is needed to validate our findings and examine the potential use of body composition assessment for dosing chemotherapeutics agents. These observations are particularly important given the relatively high prevalence of sarcopenia in this cohort of breast cancer survivors and the naturally occurring age-related loss of muscle mass, potentially accelerated by cancer, its treatment, and hormone manipulation [53–55]. Research into the development of effective interventions to maintain and/or increase skeletal muscle mass may also improve prognosis in breast cancer survivors.

Acknowledgments

The authors would like to thank Anita Ambs and Todd Gibson for their continued assistance and support, as well as the HEAL participants for their ongoing dedication to this study. This study was supported through National Cancer Institute contracts NO1-CN-75036-20, NO1-CN-05228, NO1-PC-67010, U54-CA116847, and training grant R25-CA094880. A portion of this work was conducted through the Clinical Research Center at the University of

Washington and support by the National Institutes of Health grant MO1-RR-0037 and University of New Mexico grant, NCRR MO1-RR-0997.

References

1. Chen X, et al. Obesity and weight change in relation to breast cancer survival. *Breast Cancer Res Treat.* 2010; 122(3):823–833. [PubMed: 20058068]
2. Carmichael AR. Obesity and prognosis of breast cancer. *Obes Rev.* 2006; 7(4):333–340. [PubMed: 17038127]
3. Prado CM, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res.* 2009; 15(8):2920–2926. [PubMed: 19351764]
4. Prado CM, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol.* 2008; 9(7):629–635. [PubMed: 18539529]
5. Tan BH, et al. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res.* 2009; 15(22):6973–6979. [PubMed: 19887488]
6. Gallagher D. Weight loss in older women: influences on body composition. *Am J Clin Nutr.* 2006; 84(5):957–958. [PubMed: 17093142]
7. Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr.* 1997; 127(5):990S–991S. [PubMed: 9164280]
8. Baumgartner R, et al. Epidemiology of sarcopenia among elderly in New Mexico. *Am J Epidemiol.* 1998; 147:755–763. [PubMed: 9554417]
9. Baumgartner RN. Body composition in healthy aging. *Ann N Y Acad Sci.* 2000; 904:437–448. [PubMed: 10865787]
10. Morley JE, et al. Sarcopenia. *J Lab Clin Med.* 2001; 137(4):231–243. [PubMed: 11283518]
11. Marcell TJ. Sarcopenia: causes, consequences, and preventions. *J Gerontol A Biol Sci Med Sci.* 2003; 58(10):M911–M916. [PubMed: 14570858]
12. Courneya KS, et al. Six-month follow-up of patient-rated outcomes in a randomized controlled trial of exercise training during breast cancer chemotherapy. *Cancer Epidemiol Biomarkers Prev.* 2007; 16(12):2572–2578. [PubMed: 18086760]
13. Courneya KS, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multi-center randomized controlled trial. *J clin onc: off j Amer Soc Clin Oncol.* 2007; 25(28):4396–4404.
14. Janssen I. The epidemiology of sarcopenia. *Clin Geriatr Med.* 2011; 27(3):355–363. [PubMed: 21824552]
15. Fielding RA, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International Working Group on Sarcopenia. *J Am Med Dir Assoc.* 2011; 12(4):249–256. [PubMed: 21527165]
16. Irwin ML, et al. Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. *J Clin Oncol.* 2005; 23(4):774–782. [PubMed: 15681521]
17. Prado CM, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin onc: off j Amer Assoc Canc Res.* 2007; 13(11):3264–3268.
18. WHO. Obesity: preventing and managing the global epidemic. Geneva, Switzerland: World Health Organization; 2000.
19. Stenholm S, et al. Sarcopenic obesity: definition, cause and consequences. *Curr Opin Clin Nutr Metab Care.* 2008; 11(6):693–700. [PubMed: 18827572]
20. Baumgartner RN, et al. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obes Res.* 2004; 12(12):1995–2004. [PubMed: 15687401]
21. Davison KK, et al. Percentage of body fat and body mass index are associated with mobility limitations in people aged 70 and older from NHANES III. *J Am Geriatr Soc.* 2002; 50(11):1802–1809. [PubMed: 12410898]

22. Zamboni M, et al. Sarcopenic obesity: a new category of obesity in the elderly. *Nutr, metab, cardiovasc dis: NMCD*. 2008; 18(5):388–395.
23. McTiernan A, et al. Adiposity and sex hormones in postmenopausal breast cancer survivors. *J Clin Oncol*. 2003; 21(10):1961–1966. [PubMed: 12743149]
24. Baumgartner KB, et al. Association of body composition and weight history with breast cancer prognostic markers: divergent pattern for Hispanic and non-Hispanic White women. *Am J Epidemiol*. 2004; 160(11):1087–1097. [PubMed: 15561988]
25. Link J, et al. International Classification of Diseases coding changes lead to profound declines in reported idiopathic pulmonary arterial hypertension mortality and hospitalizations: implications for database studies. *Chest*. 2011; 139(3):497–504. [PubMed: 20724737]
26. Kiebzak GM, et al. Measurement precision of body composition variables using the lunar DPX-L densitometer. *J Clin Densitom*. 2000; 3(1):35–41. [PubMed: 10745300]
27. WHO. International Statistical Classification of Diseases and Related Health Problems (10th revision). Geneva: World Health Organization; 1992.
28. Cruz-Jentoft AJ, et al. Sarcopenia: European consensus on definition and diagnosis. *Age and ageing*. 2010; 39(4):412–423. [PubMed: 20392703]
29. Rolland Y, et al. Sarcopenia, calf circumference, and physical function of elderly women: a cross-sectional study. *J Am Geriatr Soc*. 2003; 51(8):1120–1124. [PubMed: 12890076]
30. Delmonico MJ, et al. Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women. *J Am Geriatr Soc*. 2007; 55(5):769–774. [PubMed: 17493199]
31. Therneau, TM.; Grambsch, PM. Modeling survival data: extending the Cox model. *Statistics for biology and health*. New York: Springer; 2000. p. 350
32. Kleinbaum, DG.; Klein, M. Evaluating the proportional hazards assumption, in *Survival analysis a self-learning text*. New York: Springer; 2005. p. 131-171.
33. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996; 15(4):361–387. [PubMed: 8668867]
34. Charlson M, et al. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994; 47(11):1245–1251. [PubMed: 7722560]
35. Rock CL, Demark-Wahnefried W. Nutrition and survival after the diagnosis of breast cancer: a review of the evidence. *J Clin Oncol*. 2002; 20(15):3302–3316. [PubMed: 12149305]
36. Li CI, et al. Epidemiologic and molecular risk factors for contra-lateral breast cancer among young women. *Br J Cancer*. 2003; 89(3):513–518. [PubMed: 12888823]
37. Li CI, Moe RE, Daling JR. Risk of mortality by histologic type of breast cancer among women aged 50 to 79 years. *Arch Intern Med*. 2003; 163(18):2149–2153. [PubMed: 14557212]
38. Phipps, AI.; Li, CI. Breast cancer biology and clinical characteristics. In: Li, CI., editor. *Breast cancer epidemiology*. New York: Springer; 2010. p. 21-46.
39. Gurney HP, et al. Factors affecting epirubicin pharmacokinetics and toxicity: evidence against using body-surface area for dose calculation. *J Clin Oncol*. 1998; 16(7):2299–2304. [PubMed: 9667243]
40. Cosolo WC, et al. Lean body mass, body surface area and epirubicin kinetics. *Anticancer Drugs*. 1994; 5(3):293–297. [PubMed: 7919453]
41. Morgan DJ, Bray KM. Lean body mass as a predictor of drug dosage. Implications for drug therapy. *Clin Pharmacokinet*. 1994; 26(4):292–307. [PubMed: 8013162]
42. Visser M, et al. Validity of fan-beam dual-energy X-ray absorptiometry for measuring fat-free mass and leg muscle mass. Health, aging, and body composition study—Dual-Energy X-ray Absorptiometry and Body Composition Working Group. *J Appl Physiol*. 1999; 87(4):1513–1520. [PubMed: 10517786]
43. Rock CL, Demark-Wahnefried W. Can lifestyle modification increase survival in women diagnosed with breast cancer? *J Nutr*. 2002; 132(11):3504S–3507S. [PubMed: 12421877]

44. George SM, et al. Postdiagnosis diet quality, the combination of diet quality and recreational physical activity, and prognosis after early-stage breast cancer. *Canc causes & contr: CCC*. 2011; 22(4):589–598.
45. Chen X, et al. Exercise after diagnosis of breast cancer in association with survival. *Canc Prev Res (Phila)*. 2011; 4(9):1409–1418.
46. Cederholm TE, et al. Toward a definition of sarcopenia. *Clin Geriatr Med*. 2011; 27(3):341. [PubMed: 21824551]
47. Newman AB, et al. Sarcopenia: alternative definitions and associations with lower extremity function. *J Am Geriatr Soc*. 2003; 51(11):1602–1609. [PubMed: 14687390]
48. Honda H, et al. Obese sarcopenia in patients with end-stage renal disease is associated with inflammation and increased mortality. *Am J Clin Nutr*. 2007; 86(3):633–638. [PubMed: 17823427]
49. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc*. 2002; 50(5): 889–896. [PubMed: 12028177]
50. Project TIH. A haplotype map of the human genome. *Nature*. 2005; 437:1299–1320. [PubMed: 16255080]
51. Howie BN, et al. Efficient selection of tagging single-nucleotide polymorphisms in multiple populations. *Hum Genet*. 2006; 120(1):58–68. [PubMed: 16680432]
52. Wang ZM, et al. Skeletal muscle mass: evaluation of neutron activation and dual-energy X-ray absorptiometry methods. *J Appl Physiol*. 1996; 80(3):824–831. [PubMed: 8964743]
53. Cruz-Jentoft AJ, et al. Understanding sarcopenia as a geriatric syndrome. *Curr Opin Clin Nutr Metab Care*. 2010; 13(1):1–7. [PubMed: 19915458]
54. Messier V, et al. Menopause and sarcopenia: a potential role for sex hormones. *Maturitas*. 2011; 68(4):331–336. [PubMed: 21353405]
55. Beyer I, Mets T, Bautmans I. Chronic low-grade inflammation and age-related sarcopenia. *Curr Opin Clin Nutr Metab Care*. 2012; 15(1):12–22. [PubMed: 22108098]

Fig. 1.
Overall survival curves of breast cancer survivors with and without sarcopenia

Fig. 2.
Breast-cancer-specific survival curves of breast cancer survivors with and without sarcopenia

Table 1
Baseline anthropometry and body composition of breast cancer survivors by sarcopenic status (N=471)

	Distribution of sarcopenia									
	No sarcopenia (N=396)					Sarcopenia (N=75)				
	Min	5th percentile	Median	95th percentile	Max	Min	5th percentile	Median	95th percentile	Max
Age (years)	29.4	38.8	56.0	78.9	85.8	39.6	43.9	63.9	80.0	87.8
Weight (kg)	40.0	53.0	68.0	100.9	138.4	38.0	42.0	56.0	68.0	72.0
Height (cm)	145.0	151.2	162.0	174.0	179.4	147.0	149.0	161.0	170.0	175.0
Waist circumference (cm)	59.9	70.2	87.1	112.5	133.5	61.5	64.3	78.4	90.5	96.0
Body mass index (kg/m ²)	17.1	20.0	26.0	37.3	46.3	16.2	17.3	21.7	26.8	27.4
Total body fat mass (%)	6.9	22.2	39.2	49.9	54.7	15.0	23.2	35.9	43.6	47.0
Appendicular lean mass (kg)	11.9	13.8	16.9	21.0	26.0	9.5	10.5	13.5	15.3	16.3
Appendicular lean mass index (kg/m ²)	5.5	5.5	6.4	7.7	9.1	3.9	4.5	5.3	5.4	5.5
Min minimum, Max maximum										

Table 2

Associations of participant and disease characteristics by sarcopenic status

	Body composition phenotypes						P value ^d	
	No sarcopenia			Sarcopenia				
	Number	Percent		Number	Percent			
All participants	471	100.0		396	100.0	75	100.0	
Age at diagnosis (years)								0.003
<50	84	17.83		83	21.0	1	1.3	
50	387	82.17		313	79.0	74	98.7	
Adiposity, body fat percentage								0.011
Not obese: <38 %	225	47.8		179	45.2	46	61.3	
Obese: ≥ 38 %	246	52.2		217	54.8	29	38.7	
Body mass index (kg/m ²)								<0.001
Underweight (<18.5)	11	2.3		161	40.7	59	78.7	
Normal (18.5–24.9)	220	46.7		5	1.3	6	8.0	
Overweight (25–29.9)	139	29.5		129	32.6	10	13.3	
Obese (≥ 30)	101	21.4		101	25.5	0	0.0	
Race/ethnicity/geographic location								0.512
Non-Hispanic white/Washington	63	13.4		51	12.9	12	16.0	
Non-Hispanic white/New Mexico	304	64.5		253	63.9	51	68.0	
Hispanic/New Mexico	93	19.7		82	20.7	11	14.7	
Other/Washington and New Mexico	11	2.3		10	2.5	1	1.3	
Menopausal status								0.001
Pre-menopausal	143	30.4		133	33.6	10	13.3	
Post-menopausal	315	66.9		251	63.4	64	85.3	
Moderate/vigorous physical activity, 7+h/week								0.378
No	346	73.5		294	74.2	52	69.3	
Yes	125	26.5		102	25.8	23	30.7	
Alcohol intake, 2+ beverages/day								0.411
No	280	59.4		239	60.4	41	54.7	
Yes	13	2.8		10	2.5	3	4.0	

	Body composition phenotypes						P value ^a	
	No sarcopenia			Sarcopenia				
	Number	Percent		Number	Percent			
Unknown	178	37.8		147	37.1	31	41.3	0.839
Current Smoker (%)								
No	424	90.0		356	89.9	68	90.7	
Yes	47	10.0		40	10.1	7	9.3	0.213
Charlson comorbidity Score								
0	409	86.8		339	85.6	70	93.3	
1	54	11.5		50	12.6	4	5.3	0.185
2	8	1.7		7	1.8	1	1.3	
Treatment type								
Surgery only	117	24.8		93	23.5	24	32.0	0.308
Surgery and radiation	195	41.4		162	40.9	33	44.0	
Surgery and chemotherapy	37	7.9		32	8.1	5	6.7	
Chemotherapy and radiation	122	25.9		109	27.5	13	17.3	0.048
Tamoxifen use								
No	252	53.5		216	54.5	36	48.0	
Yes	214	45.4		176	44.4	38	50.7	0.003
Tumor stage								
Localized	362	76.9		298	75.3	64	85.3	
Regional	109	23.1		98	24.7	11	14.7	0.003
Nodal involvement								
None/unknown	309	65.6		257	64.9	52	69.3	
1	113	24.0		104	26.3	9	12.0	0.003
None examined	49	10.4		35	8.8	14	18.7	

Not all sum to 100 % due to missing values

^a P value represents test for variation across specific characteristics

Table 3
Hazard ratios and 95 % CIs for risk of death from any cause with sarcopenia (N=471)

Models of association of sarcopenic status and death from any cause	No sarcopenia (N=396)		Sarcopenia (N=75)		P value ^a
	HR	95 % CI	HR	95 % CI	
Death, any cause	68 deaths		24 deaths		
Age-adjusted	1.0 (referent)		1.90	1.17 3.08	
Multivariable					
Model 1	1.0 (referent)		2.44	1.44 4.15	
Model 2	1.0 (referent)		2.86	1.67 4.89	<0.001
Model 3	1.0 (referent)		2.29	1.34 3.90	0.192
Model 4	1.0 (referent)		2.86	1.67 4.90	0.001
Model 5	1.0 (referent)		2.77	1.61 4.77	<0.001

HR hazard ratio, 95 % CI 95 % confidence interval, BMI body mass index, Mod/Vig moderate/vigorous

Model 1 adjusts for age, race/ethnicity with center site, treatment, Charlson comorbidity score, and waist circumference. Model 2 adjusts for model 1 covariates plus body fat percentage. Model 3 adjusts for model 1 covariates plus BMI. Model 4 adjusts for model 1 covariates with body fat percentage plus tumor stage. Model 5 adjusts for model 1 covariates with body fat percentage plus physical activity

^a P-value associated with change in likelihood seen in nested models including and excluding additional model group variables for model 1

Table 4Hazard ratios and 95 % CIs for risk of death from breast cancer with sarcopenia ($N=471$)

Models of association of sarcopenic status and death from breast cancer	No sarcopenia ($N=396$)	Sarcopenia ($N=75$)		
		HR	95 % CI	
Death, breast cancer	37 deaths		9 deaths	
Age-adjusted	1.0 (referent)	1.65	0.78	3.52
Multivariable ^a	1.0 (referent)	1.95	0.87	4.35

HR hazard ratio, *95% CI* 95 % confidence interval^a Model adjusted for age, race/ethnicity with center site, treatment, tamoxifen use, disease stage, and waist circumference