LOYOLA UNIVERSITY CHICAGO 1870 AD MAJOREM DEI GLORIAM eCOMMONS

Loyola University Chicago
Loyola eCommons

Nursing: School of Nursing Faculty Publications and Other Works

Faculty Publications and Other Works by Department

4-2018

Prevalence and Predictors of Low Serum 25-Hydroxyvitamin D among Female African-American Breast Cancer Survivors

Patricia M. Sheean
Loyola University Chicago, psheean1@luc.edu

Claudia Arroyo

Jennifer Woo

Melinda Stolley

Follow this and additional works at: https://ecommons.luc.edu/nursing_facpubs

 Part of the Nursing Commons, and the Oncology Commons

Recommended Citation

Sheean, Patricia M.; Arroyo, Claudia; Woo, Jennifer; and Stolley, Melinda. Prevalence and Predictors of Low Serum 25-Hydroxyvitamin D among Female African-American Breast Cancer Survivors. Journal of the Academy of Nutrition and Dietetics, 118, 4: 568-577, 2018. Retrieved from Loyola eCommons, Nursing: School of Nursing Faculty Publications and Other Works, http://dx.doi.org/10.1016/j.jand.2017.10.009

This Article is brought to you for free and open access by the Faculty Publications and Other Works by Department at Loyola eCommons. It has been accepted for inclusion in Nursing: School of Nursing Faculty Publications and Other Works by an authorized administrator of Loyola eCommons. For more information, please contact ecommons@luc.edu.

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 3.0 License.
© Academy of Nutrition and Dietetics 2018

Title: Prevalence and predictors of low serum 25(OH)D among female African-American breast cancer survivors

Research Snapshot:

Research Questions:

What is the prevalence of low serum 25(OH)D among female African American (AA) breast cancer (BC) survivors? What modifiable factors are significant predictors of serum 25(OH)D levels in these minority women?

Key Findings:

In this cross-sectional study comprised of 244 early stage AA BC survivors with overweight/obesity, vitamin D deficiency was prevalent in 81% and 43% of women, applying the cut-points of the Endocrine Society (<30 ng/ml or <75 nmol/L) and the Institute of Medicine (<20 ng/ml or <50 nmol/L), respectively. Interestingly, 60% of participants endorsed habitual use of vitamin D supplementation. In multivariate modeling, Vitamin D supplementation, sun behaviors and waist hip ratio were significant predictors of serum 25(OH)D levels and thus, may serve as future points of intervention to improve the vitamin D status of this minority survivor population.

Abstract

Background: African-American (AA) breast cancer (BC) survivors commonly demonstrate low serum 25(OH)D. Decreased cutaneous conversion, high levels of adiposity and even BC treatment may influence vitamin D status. Previous investigations have analyzed AA women in aggregate with other BC survivors and have not comprehensively addressed these influential factors.

Objective: To determine the prevalence of low serum 25(OH)D in an exclusively AA cohort of female BC survivors with overweight/obesity. And further, to evaluate the role of ultraviolet (UV) light exposure, body composition, and dietary sources of vitamin D on serum 25(OH)D levels.

Design: Cross-sectional

Participants: Pre- and post-menopausal AA BC survivors (n=244) were recruited from various neighborhoods in the city of Chicago between September, 2011 – September, 2014 for a larger weight loss trial.

Main outcome measures: Demographic, clinical, anthropometric [body mass index (BMI), waist (WC) and hip circumference (HC)], blood biospecimen, dietary intake [Food frequency questionnaire (FFQ)] and sun behavior data were collected by trained study personnel prior to trial participation. Dual energy x-ray absorptiometry (DXA) was used to quantify adiposity (total, %, regional, visceral) and lean mass. Serum 25(OH)D was used as the biomarker reflective of vitamin D status.

Statistical analyses: Mean (± standard deviation), frequencies and multivariate linear regression modeling

Results: The average participant was 57.4 (± 10.0) y, 6.9 (± 5.2) y from initial BC diagnosis with a BMI of 36.2 (± 6.2) kg/m^2. The majority of participants (60%) reported habitual oral vitamin D supplementation with mean intakes of 327 (± 169) IUs. Vitamin D deficiency was prevalent in 81% and 43%, applying the cut-points of the Endocrine Society (<30 ng/ml or <75 nmol/L) and the Institute of Medicine (<20 ng/ml or <50 nmol/L), respectively. A multivariate model adjusting for age, seasonality of blood draw, total energy intake, supplemental vitamin D, darker skin pigmentation, BC stage and waist hip ratio (WHR) was able to explain 28.8% of the observed variance in serum 25(OH)D concentrations. No significant associations were detected for BMI or any DXA measures of body composition.

Conclusions:

Considering the number of women endorsing the use of vitamin D supplementation, the prevalence of vitamin D deficiency among these AA BC survivors was high. Vitamin D supplementation, sun behaviors and WHR may serve as future points of intervention to improve the vitamin D status of this minority survivor population.

INTRODUCTION

Vitamin D is a generic term designating a group of chemically related compounds best known for their antirachtic activity. Serum 25(OH)D is the generally accepted biomarker for determining vitamin D status.[1] It is well known that serum 25(OH)D is derived from sun exposure and that dietary sources of vitamin D (e.g., egg yolks, salmon, tuna, and fortified dairy products) contribute less significantly to these levels.[2] Because vitamin D influences the expression of genes that are associated with the development and progression of breast cancer (BC),[3,4] intensive efforts over the last two decades have sought to elucidate the role of 25(OH)D, BC occurrence and BC outcomes.

While the exact mechanisms remain unknown, BC treatment, itself, appears to be associated with lower levels of serum 25(OH)D. Approximately 70-75% of female BC survivors are classified as vitamin D deficient/insufficient,[5-7] which is higher than population estimates.[8] These previous BC studies, while informative, are limited by two notable factors. First, the majority of BC survivors enrolled were non-Hispanic white with relatively small numbers of African American (AA) BC participants by comparison. Decreased cutaneous conversion of 7-dehydrocholesterol to cholecalciferol occurs with higher melanin content.[9] Accounting for skin pigmentation and sun behaviors are informative, yet understudied areas in the context of serum 25(OH)D and BC. Second, body mass index (BMI) has been used a surrogate marker of adiposity.[10,11] This approach is an attempt to address the inverse relationship between obesity and 25(OH)D.[11] However, a systematic review and meta-analyses of 31,968 participants reveals that BMI fails to detect half of the people with excess adiposity;[12] thus its

application as a surrogate marker for adiposity is questionable. Therefore, the objective of this investigation is to examine serum 25(OH)D levels in an exclusively AA cohort of female BC survivors with overweight/obesity. The present study is novel, in that, it simultaneously addresses important non-modifiable (i.e., BC treatment, sex, race/ethnicity) and modifiable factors (e.g., sun exposure, adiposity) using methodologies that can accurately measure body composition and tools that can capture important contributors to serum 25(OH)D, such as skin color or sun behaviors. This study addresses notable shortcomings of previous work in an effort to more precisely establish the prevalence and predictors of low serum 25(OH)D and to identify potential intervention points among these minority BC survivors. We hypothesize that the majority of the participants will be classified as vitamin D deficient, and that darker skin pigmentation and higher levels of percent body fat will negatively predict serum levels of 25(OH)D.

METHODS

Study participants

Study participants reflect AA BC survivors recruited from various communities within Chicago, Illinois between September, 2011 – September, 2014 for a larger randomized behavioral weight loss trial. These present analyses use a cross-sectional study design of data collected at baseline for prevalence estimates. The specific study methodologies have been described previously.[13] Briefly, eligible adult women: 1) self-identified as Black or AA females; 2) self-reported Stage I-III invasive breast carcinoma; 3) were overweight (BMI 25.0-29.9 kg/m^2) or obese (BMI $\geq$30.0 kg/m^2), and 4) completed surgery, chemotherapy and/or radiation treatment at least six months *prior to*

recruitment. Current use of adjuvant hormonal therapies was acceptable. Women were excluded for the following: 1) plans to relocate out of the Chicago area during the time of study participation, 2) unable to safely engage in physical activity due to physical impairments requiring a wheelchair or walker, a diagnosis of emphysema or extreme dyspnea on exertion, 3) currently pregnant, planning to get pregnant or less than 3 months post-partum, 4) formally enrolled in a weight loss program requiring specialty foods or meal replacements, 5) taking prescription weight loss agents; or 6) experiencing any psychiatric conditions that precluded study participation. The study received ethical approval from the Institutional Review Boards of the University of Illinois, University of Chicago and Northwestern University.

Procedures

Women were screened for initial eligibility over the telephone by the study recruiters. (**Figure 1**) A baseline interview was scheduled for eligible women, written informed consent was obtained and variety of questionnaires were completed. Within one month of the baseline interview, eligible/interested women returned for blood draw, anthropometric measures and DXA completion.

Data collection

Demographic and clinical data, including co-morbid conditions, menopausal status, BC stage, date of diagnosis, BC treatments [e.g., chemotherapy (yes/no), radiation (yes/no), current or previous endocrine therapies [selective estrogen receptor modulators or aromatase inhibitors] and other medications were self-reported. Oncologists were contacted to verify disease stage, when needed. Women with Stage 0 or IV were precluded further participation.

Phlebotomy and body composition assessment were completed on the same day prior to participation in the weight loss trial. Blood draws were completed by trained phlebotomists, transported and processed by a certified clinical laboratory on the same day. The best marker for vitamin D status is serum 25(OH)D, which is comprised of $25(OH)D_3$ and $25(OH)D_2$.[1,14] Serum 25(OH)D levels were quantified using the DiaSorin Liaison 25 OH vitamin D total assay, which uses chemiluminescent immunoassay technology for the quantitative determination of 25(OH)D and other hydroxylated vitamin D metabolites.

Height was measured to the nearest 0.1 cm using a portable stadiometer (Seca 213; Chino, CA) and weight was measured to the nearest 0.1 kg using a digital scale (Tanita BWB 800S; Arlington Heights, IL). Participants wore light clothes and were measured without shoes. Measurements were obtained by trained study personnel. If two measurements were more than 0.5 cm or 0.2 kg apart for height and weight, respectively, a third measurement was taken. The two closest measures of height and weight were used to calculate and classify BMI (kg/m^2).[15]

Waist and hip measures, surrogate measures of visceral and gluteal adiposity, respectively, were completed by trained study staff based on the National Health and Nutrition Examination Survey techniques.[16] However, the umbilicus was used as the external marker for waist circumference (WC). Waist and hip circumference were measured by placing a Gulick II Plus measuring tape in the horizontal plane (parallel to the floor) around the abdomen at the umbilicus for WC or at the widest point over the buttocks for hip circumference (HC). Participants were told to wear light clothing to allow direct measurement on the skin, assuring the removal or minimum inclusion of bulky

clothing (e.g., seams, gathered material from pants, shirts or other garments) in the measurement. Participants were further instructed to breathe normally and stand with ankles as close together as possible. A second staff member ensured that the measuring tape was parallel to the floor with measurements taken in duplicate to the nearest 0.1 cm and recorded. Additional measurements were taken and recorded until two measurements were within 1.0 cm of each other.

Body composition was measured using DXA (iLunar, GE, software version 13.6). **(Figure 2)** Following daily calibration with the manufacturer's phantom, whole body scans were performed and analyzed by a trained technician blind to study group or outcomes. For measuring android fat, a region of interest was automatically defined using the methods of Kaul et al.[17] Abdominal and visceral were obtained from the android region. Random whole body and hip images were periodically reviewed by a certified bone densitometrist for quality assurance purposes. Errors were corrected, techniques were altered to prevent future errors, and images were reanalyzed as needed prior to download and statistical analyses.

The Block 2005 Food Frequency Questionnaire (FFQ), a validated,[18] 110-item dietary assessment tool, was administered in person by trained personnel and processed by NutritionQuest (Berkeley, CA) to procure habitual dietary intakes reflective of the previous 6 months for vitamin D from food, beverage and dietary supplements sources. To account for important, non-dietary sources of vitamin D, we quantified summer sunlight exposure (focusing on weekend and weekday 'hours outside'), addressed seasonal influence of blood draw (i.e., participants drawn June- September

vs. October-May) and we categorized participants into one of six levels of self-reported skin pigmentation.[19]

STATISTICAL ANALYSES

Because of the current lack of agreement on levels used to classify deficiency, serum 25(OH)D cut-points proposed by, both, the Endocrine Society[20] and the Institute of Medicine (IOM),[21] were applied. Means, medians, standard deviations, and ranges were used to describe the distribution of the data. Non-normally distributed variables were log transformed for analyses. Student's *t* and Wilcoxon rank-sum tests for continuous variables and Chi square for categorical variables were conducted for comparisons between deficient and non-deficient participants. Multivariate linear regression analyses were conducted to determine the characteristics that independently predicted serum 25(OH)D, after adjustment for other variables. Informed by our preliminary analyses and previous studies, several covariates were included in the models due to their abilities to predict serum 25(OH)D (e.g., age, seasonality of blood draw, diet/supplement contribution.) Reasoning that dark skin would impede ultraviolet light the most, self-reported untanned skin was reduced to a two categories ["dark" (i.e., dark brown and very dark) vs. "light" (very fair, fair, olive and light brown)]. Variables were only retained in the multivariate models if the effect of the variable changed the point estimate by >10% or if the variable was significant in the multivariate model ($p \leq 0.05$). Collinearity was assessed prior to the final modeling and only one variable was selected for model fitting (e.g., dietary vitamin D vs. total energy intake, visceral adipose tissue (VAT) mass vs. android fat mass). Statistical analysis was conducted using the statistical program SAS (version 9.4).[22]

RESULTS

The average age of the participants (N=244) was 57.4 y (±10.0) and 11% (n=27) had overweight (BMI 25.0-29.9), 23% (n=99) had Class 1 obese (BMI 30.0-34.9), 26% (n=63) had Class 2 obese (35.0-39.9) and 40% (n=55) had Class 3 obese (BMI ≥ 40.0). Participants were predominantly non-smokers (91%, n= 219), diversely educated [39% (n= 95) completed some college and 38% (n= 93) possessed a college and/or graduate degree] and 50% (n=122) were privately insured. The average body weight, BMI and WHR was 96.1 (±18.2) kg, 36.2 (±6.2) kg/m^2 and 0.94 (±0.09), respectively. Self-reports of diabetes, high blood pressure and high serum cholesterol were 53%, 59% and 38%, respectively, signifying an overall high prevalence of co-morbid conditions. The average time since BC diagnosis was 6.9 (±5.2) y, with 73% (n=175) and 79% (n=189) of women self-reporting previous chemotherapy or radiation treatment, respectively.

The demographic and clinical characteristics of the study participants stratified by vitamin D cut-points are presented in **Table 1.** The mean serum 25(OH)D was 22.5 (±10.8) mg/dL [56.2 (±27.0)]. The prevalence of vitamin D deficiency was 81% and 43% using the values of the Endocrine Society and IOM, respectively. Individuals classified as vitamin D sufficient by Endocrine society tended to be older at the time of study enrollment (p=0.003) and at BC diagnosis (p=0.02), reported a lower occurrence of diabetes (p=0.017) and hypertension (p=0.002) and were more often employed fulltime or retired when compared to individuals classified as insufficient. Individuals classified as vitamin D sufficient using the IOM cut-points were older at the time of BC diagnosis (p=0.037) and more likely to report early disease stage (p=0.001) and hypertension (p=0.025).

Table 2 depicts the bivariate analyses of potential predictors of serum 25(OH)D using dichotomized definitions of vitamin D status. Due to changes from a shorter to a longer version of the FFQ, only dietary data from recruitment sites 2-8 were evaluable (n=219). When stratified by the Endocrine Society cut-points, participants who were classified as insufficient reported darker skin pigmentation (p= 0.01). When stratified by the IOM cut-points, participants who were classified as insufficient had higher android fat mass measurements (p<0.001), higher energy (p<0.001) and dietary vitamin D intake (p<0.001). In addition, mean serum 25(OH)D levels were significantly higher for participants who had blood draws in June-September vs. October-May (24.6 ± 10.8 vs. 21.2 ± 10.7, respectively; p=0.02).

Linear regression modeling involved examining the associations between lifestyle, clinical and BC treatment related variables with log transformed serum 25(OH)D. Significant independent associations between serum 25(OH)D and age (β= 0.00868; p=0.008), dietary vitamin D, IU (β= -0.001; p= 0.05), vitamin D supplementation, IU (β= 0.00111; p<0.001), total energy intake, kcals (β= -0.00013; p<0.001) and seasonality of blood draw (β= 0.20384; p=0.002) were detected. None of the variables related to BC disease status or treatment (alone or in combination) were independently associated with serum 25(OH)D (p >0.05). Initially, the following body composition variables were inversely associated with serum 25(OH)D: weight (p= 0.02), waist (p=0.03), total fat mass (p=0.02), VAT mass (p=0.04), android fat mass (p=0.01), gynoid fat mass (p=0.04), total lean mass (p=0.02) and ALH (p=0.04). Linear regression modeling involved assessing the effects of the various body composition variables on log transformed serum 25(OH)D. Our final multivariate model was able to explain 28.8% of

the observed variance in serum 25(OH)D concentrations, adjusting for age (β= 0.00049), seasonality of blood draw (β= 0.15096), total energy intake, kcals (β= -0.00011), supplemental vitamin D (β= 0.00107), darker skin pigmentation (β= -0.08668), and BC stage (β= -11236) and WHR (β= -0.79472). No significant associations were detected for BMI or any DXA measures of body composition.

DISCUSSION

The interpretation of our study findings is not straightforward owing to the variation in how vitamin D deficiency is defined. When we apply the more conservative IOM cut-point of <20 ng/ml (<50 nmol/L), we found that 43% of our AA female BC survivors were classified as vitamin D deficient. Considering that 82% of AAs (≥ 20 years of age) participating in the NHANES are classified as vitamin D deficient,[23] we view our results as discrepant, yet positive. However, when we apply the more liberal cut-point of the Endocrine Society (<30 ng/ml or <75 nmol/L), our prevalence of vitamin D deficiency increases to 81%. The occurrence of low serum 25(OH)D is 35-77% using a similar cut-point (<30-32 ng/ml) in predominantly non-minority BC survivors,[5-7,24] reflecting lower prevalence estimates than our AA BC population. Regardless of these deficiency definitions, observational data support an inverse relationship between higher serum 25(OH)D at diagnosis and lower risk for BC progression and mortality.[25] Specifically, in an observational cohort of 512 early stage BC survivors, Goodwin et al showed that low plasma levels of 25(OH)D (<20 ng/ml or <50 nmol/L) at the time of BC diagnosis were significantly associated with an increased risk of distant recurrence and death.[26] These effects were only modestly attenuated after adjustment for tumor-related factors. A more recent systematic review and meta-analysis (n=5,691) indicated that low

blood levels of serum (OH)D were associated with a pooled hazard ratio of 2.1 (95% CI 1.6, 2.8) for recurrence and 1.8 (95% CI 1.4, 2.3) for mortality in women diagnosed and previously treated for early stage BC.[27] Thus, many BC survivors are prescribed supplemental vitamin D under the clinical presumption that it will positively influence BC survivorship. It is clear that many of our participants 'heard this message' since 60% of those with evaluable dietary data (n=132) reported ingesting supplemental vitamin D; a significant predictor of serum 25(OH)D ($p<0.001$). Based on our deficiency levels, AA BC survivors may require higher doses to achieve a therapeutic response. Taking into account our cross-sectional design and the length of time since initial BC diagnosis, we cannot, however, extrapolate our findings to make assumptions regarding the survivorship of our participants. Although, vitamin D deficiency has been hypothesized to contribute to risk of more aggressive BC in AA women,[28] the possibility that AA BC survivors with lower serum 25(OH)D experienced metastasis or mortality closer to the time of BC diagnosis would have precluded study participation, posing important confines on these data.

In previous studies, BMI was a significant, inverse predictor of serum 25(OH)D,[29-34] perhaps due to vitamin D sequestration into the adipose tissue, alterations in metabolism from hepatic steatosis or inhibitory effects of adipokines.[11] Body composition is a developing science that examines more than BMI, specifically accounting for the amount and location of adipose and lean tissue compartments in the human body.[35] Due to recent advances, the precision with which to measure body composition has substantially increased over the last two decades.[36] Despite the known validity and reliability of DXA in individuals who are lean or obese, [37,38] the current study

did not find significant associations between serum 25(OH)D and DXA quantified measures of body composition in our cohort of AA BC survivors with overweight/obesity. Regardless, this relationship is inconsistent in AA populations,[39-41] which is supported by our study findings. Due to the high prevalence of central obesity in our participants, we anticipated that VAT would have negatively predicted serum 25(OH)D levels. A growing body of literature now highlights that AA women may possess higher WC, yet lower levels of VAT when compared to women of other race/ethnicities.[42-46] Interestingly, only WHR, a surrogate marker of android vs. gynoid adiposity, was a significant determinant of serum 25(OH)D, accounting for 5% of its variability ($p=0.0279$). This lack of consistency highlights two concerns. First, WC measures were taken at the level of the umbilicus. This physical landmark may not always align with the DXA defined regions of interest for VAT assessment. Second, while DXA provides estimates of VAT, more importantly, it cannot parse out the deep vs. superficial subcutaneous adipose tissues. These tissue compartments are only measureable using computed tomography or magnetic resonance imaging, but are emerging as distinctly different predictors of metabolic risk.[47]

Many assays are utilized to quantify 25(OH)D and these can be generally grouped into 2 categories: immune based and chromatography based.[14,48] Due to superior precision, liquid chromatography tandem mass spectrometry is considered the 'gold standard' and as such, used a reference measure in comparison studies.[14,49-52] Because immunoassays procedures are easily automated, considerably less expensive and readily available, these methods are most widely used in clinical facilities and practice. Unfortunately, immunoassays have variable specificity for $25(OH)D_2$,

309 25(OH)D_3, the C3-epimer of 25(OH)D and other 25(OH)D metabolites,[53] reducing
310 measurement accuracy as much as 20%.[54] Acknowledging this lack of agreement is
311 important for researchers as it poses serious challenges to explore purported
312 associations between low serum 25(OH)D, non-skeletal chronic diseases (e.g., cancer)[1]
313 and relevant cancer outcomes (i.e., BC recurrence, mortality).[27]

314 Several limitations of this investigation merit discussion. First, this study involved
315 AA BC survivors with overweight/obesity who desired weight loss. While the majority of
316 AAs in the US population are overweight/obese reflecting good generalizability,[55] we did
317 not have a proportion of AA women with normal BMI or normal adiposity (<32%)[56] for
318 more rigorous comparisons. Second, we did not have measures of parathyroid
319 hormone; a known determinant of serum 25(OH)D.[1] Third, all of our participants were
320 BC survivors who had received BC treatment; thus, by design, these findings are only
321 generalizable to other AA BC survivors. Fourth, we were unable to include the dietary
322 data from our first recruitment site (n=25 women) due to changes in dietary assessment
323 methodologies. However, based on similarities across recruitment sites, we have no
324 reason to believe these dietary data would be significantly different than the other
325 participants. Additionally, this change resulted in missing data related to current
326 smoking status. Based on data reflective of 90% of the study sample (n=216), no
327 relationship between serum 25(OH)D and current smoking was detected in univariate
328 and multivariable modeling. Finally, the likelihood of Type 2 error cannot be ruled out.
329 However, sensitivity analyses showed no correlation between serum 25(OH)D and
330 percent body fat (r= -0.07, p=0.28). There were no linear and nonlinear visual patterns
331 detected between the two measures.

CONCLUSION

The determination and interpretation of serum 25(OH)D status is complex. It reflects a clinical scenario plagued by non-harmonious definitions[20,21] and employs methodologies that possess laboratory drift and variation.[57] Applying the cut-points of the Endocrine Society and the IOM, we found that vitamin D deficiency was prevalent in 81% and 43% of our AA BC survivors with overweight/obesity, respectively. While, skin pigmentation, age and BC stage are not modifiable, vitamin D supplementation, sun behaviors and WHR are all significant predictors of serum 25(OH)D levels and thus may serve as potential future points of intervention to improve the vitamin D status of this minority survivor population.

References

1. Holick MF. Vitamin D deficiency. *The New England journal of medicine.* 2007;357(3):266-281.
2. Lips P. Worldwide status of vitamin D nutrition. *J Steroid Biochem Mol Biol.* 2010;121(1-2):297-300.
3. Chen WY, Bertone-Johnson ER, Hunter DJ, Willett WC, Hankinson SE. Associations between polymorphisms in the vitamin D receptor and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2005;14(10):2335-2339.
4. Wu X, Zhou T, Cao N, Ni J, Wang X. Role of Vitamin D Metabolism and Activity on Carcinogenesis. *Oncol Res.* 2014;22(3):129-137.
5. Neuhouser ML, Sorensen B, Hollis BW, et al. Vitamin D insufficiency in a multiethnic cohort of breast cancer survivors. *The American journal of clinical nutrition.* 2008;88(1):133-139.
6. Trukova KP, Grutsch J, Lammersfeld C, Liepa G. Prevalence of vitamin d insufficiency among breast cancer survivors. *Nutr Clin Pract.* 2012;27(1):122-128.
7. Villasenor A, Ballard-Barbash R, Ambs A, et al. Associations of serum 25-hydroxyvitamin D with overall and breast cancer-specific mortality in a multiethnic cohort of breast cancer survivors. *Cancer Causes Control.* 2013;24(4):759-767.
8. Schleicher RL, Sternberg MR, Lacher DA, et al. The vitamin D status of the US population from 1988 to 2010 using standardized serum concentrations of 25-hydroxyvitamin D shows recent modest increases. *The American journal of clinical nutrition.* 2016;104(2):454-461.
9. Piotrowska A, Wierzbicka J, Zmijewski MA. Vitamin D in the skin physiology and pathology. *Acta Biochim Pol.* 2016;63(1):89-95.
10. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *The American journal of clinical nutrition.* 2000;72(3):690-693.
11. Cipriani C, Pepe J, Piemonte S, Colangelo L, Cilli M, Minisola S. Vitamin d and its relationship with obesity and muscle. *Int J Endocrinol.* 2014;2014:841248.
12. Okorodudu DO, Jumean MF, Montori VM, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. *Int J Obes (Lond).* 2010;34(5):791-799.
13. Stolley MR, Sharp LK, Fantuzzi G, et al. Study design and protocol for moving forward: a weight loss intervention trial for African-American breast cancer survivors. *BMC Cancer.* 2015;15(1):1018.
14. Zerwekh JE. Blood biomarkers of vitamin D status. *The American journal of clinical nutrition.* 2008;87(4):1087S-1091S.
15. Prevention CfDCa. Classifications of Obesity, Overweight and Underweight Adults. https://www.cdc.gov/nccdphp/dnpao/growthcharts/training/bmiage/page4.html. Accessed July 20, 2017.
16. Prevention. CCfDCa. http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf. Accessed April 6, 2017.
17. Kaul S, Rothney MP, Peters DM, et al. Dual-energy X-ray absorptiometry for quantification of visceral fat. *Obesity (Silver Spring).* 2012;20(6):1313-1318.
18. Mares-Perlman JA, Klein BE, Klein R, Ritter LL, Fisher MR, Freudenheim JL. A diet history questionnaire ranks nutrient intakes in middle-aged and older men and women similarly to multiple food records. *The Journal of Nutrition.* 1993;123(3):489-501.
19. Glanz K, Yaroch AL, Dancel M, et al. Measures of sun exposure and sun protection practices for behavioral and epidemiologic research. *Arch Dermatol.* 2008;144(2):217-222.

20. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism.* 2011;96(7):1911-1930.
21. Institute of Medicine Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press; 2010.
22. *SAS* [computer program]. Version 9.4, 2002-2012: SAS Institute, INC., Cary, NC.
23. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res.* 2011;31(1):48-54.
24. Friedman CF, DeMichele A, Su HI, et al. Vitamin d deficiency in postmenopausal breast cancer survivors. *Journal of women's health.* 2012;21(4):456-462.
25. Jacobs ET, Kohler LN, Kunihiro AG, Jurutka PW. Vitamin D and Colorectal, Breast, and Prostate Cancers: A Review of the Epidemiological Evidence. *J Cancer.* 2016;7(3):232-240.
26. Goodwin PJ, Ennis M, Pritchard KI, Koo J, Hood N. Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer. *J Clin Oncol.* 2009;27(23):3757-3763.
27. Rose AA, Elser C, Ennis M, Goodwin PJ. Blood levels of vitamin D and early stage breast cancer prognosis: a systematic review and meta-analysis. *Breast Cancer Research and Treatment.* 2013;141(3):331-339.
28. Yao S, Ambrosone CB. Associations between vitamin D deficiency and risk of aggressive breast cancer in African-American women. *J Steroid Biochem Mol Biol.* 2013;136:337-341.
29. Chan J, Jaceldo-Siegl K, Fraser GE. Determinants of serum 25 hydroxyvitamin D levels in a nationwide cohort of blacks and non-Hispanic whites. *Cancer Causes Control.* 2010;21(4):501-511.
30. McCullough ML, Weinstein SJ, Freedman DM, et al. Correlates of circulating 25-hydroxyvitamin D: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *American journal of epidemiology.* 2010;172(1):21-35.
31. Jacobs ET, Thomson CA, Flatt SW, Newman VA, Rock CL, Pierce JP. Correlates of 25-hydroxyvitamin D and breast cancer stage in the Women's Healthy Eating and Living Study. *Nutr Cancer.* 2013;65(2):188-194.
32. Lagunova Z, Porojnicu AC, Lindberg F, Hexeberg S, Moan J. The dependency of vitamin D status on body mass index, gender, age and season. *Anticancer Res.* 2009;29(9):3713-3720.
33. Vashi PG, Lammersfeld CA, Braun DP, Gupta D. Serum 25-hydroxyvitamin D is inversely associated with body mass index in cancer. *Nutr J.* 2011;10:51.
34. Shirazi L, Almquist M, Malm J, Wirfalt E, Manjer J. Determinants of serum levels of vitamin D: a study of life-style, menopausal status, dietary intake, serum calcium, and PTH. *BMC Womens Health.* 2013;13:33.
35. Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. *Jpen.* 2014;38(8):940-953.
36. Baracos V, Caserotti P, Earthman CP, et al. Advances in the science and application of body composition measurement. *Jpen.* 2012;36(1):96-107.
37. Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: advances in models and methods. *Annual review of nutrition.* 1997;17:527-558.
38. Micklesfield LK, Goedecke JH, Punyanitya M, Wilson KE, Kelly TL. Dual-energy X-ray performs as well as clinical computed tomography for the measurement of visceral fat. *Obesity (Silver Spring).* 2012;20(5):1109-1114.
39. Looker AC. Body fat and vitamin D status in black versus white women. *The Journal of clinical endocrinology and metabolism.* 2005;90(2):635-640.
40. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and

Nutrition Examination Survey, 1988-1994. *The American journal of clinical nutrition.* 2002;76(1):187-192.
41. Samuel L, Borrell LN. The effect of body mass index on adequacy of serum 25-hydroxyvitamin D levels in US adults: the National Health and Nutrition Examination Survey 2001 to 2006. *Ann Epidemiol.* 2014;24(10):781-784.
42. Carroll JF, Chiapa AL, Rodriquez M, et al. Visceral fat, waist circumference, and BMI: impact of race/ethnicity. *Obesity (Silver Spring).* 2008;16(3):600-607.
43. Katzmarzyk PT, Heymsfield SB, Bouchard C. Clinical utility of visceral adipose tissue for the identification of cardiometabolic risk in white and African American adults. *The American journal of clinical nutrition.* 2013;97(3):480-486.
44. Conway JM, Yanovski SZ, Avila NA, Hubbard VS. Visceral adipose tissue differences in black and white women. *The American journal of clinical nutrition.* 1995;61(4):765-771.
45. Kanaley JA, Giannopoulou I, Tillapaugh-Fay G, Nappi JS, Ploutz-Snyder LL. Racial differences in subcutaneous and visceral fat distribution in postmenopausal black and white women. *Metabolism.* 2003;52(2):186-191.
46. Bi X, Seabolt L, Shibao C, et al. DXA-measured visceral adipose tissue predicts impaired glucose tolerance and metabolic syndrome in obese Caucasian and African-American women. *European journal of clinical nutrition.* 2015;69(3):329-336.
47. Golan R, Shelef I, Rudich A, et al. Abdominal superficial subcutaneous fat: a putative distinct protective fat subdepot in type 2 diabetes. *Diabetes care.* 2012;35(3):640-647.
48. Fraser WD, Milan AM. Vitamin D assays: past and present debates, difficulties, and developments. *Calcif Tissue Int.* 2013;92(2):118-127.
49. Moon HW, Cho JH, Hur M, et al. Comparison of four current 25-hydroxyvitamin D assays. *Clinical biochemistry.* 2012;45(4-5):326-330.
50. Farrell CJ, Martin S, McWhinney B, Straub I, Williams P, Herrmann M. State-of-the-art vitamin D assays: a comparison of automated immunoassays with liquid chromatography-tandem mass spectrometry methods. *Clinical chemistry.* 2012;58(3):531-542.
51. van den Ouweland JM, Beijers AM, Demacker PN, van Daal H. Measurement of 25-OH-vitamin D in human serum using liquid chromatography tandem-mass spectrometry with comparison to radioimmunoassay and automated immunoassay. *Journal of chromatography B, Analytical technologies in the biomedical and life sciences.* 2010;878(15-16):1163-1168.
52. Lai JK, Lucas RM, Banks E, Ponsonby AL, Ausimmune Investigator G. Variability in vitamin D assays impairs clinical assessment of vitamin D status. *Internal medicine journal.* 2012;42(1):43-50.
53. Farrell C, Soldo J, Williams P, Herrmann M. 25-Hydroxyvitamin D testing: challenging the performance of current automated immunoassays. *Clin Chem Lab Med.* 2012;50(11):1953-1963.
54. Binkley N, Wiebe D. Clinical controversies in vitamin D: 25(OH)D measurement, target concentration, and supplementation. *J Clin Densitom.* 2013;16(4):402-408.
55. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in Obesity Among Adults in the United States, 2005 to 2014. *JAMA.* 2016;315(21):2284-2291.
56. Fitness A. 2016; http://www.acefitness.org/acefit/healthy_living_tools_content.aspx?id=2. Accessed December 1, 2016.
57. Ganji V, Zhang X, Tangpricha V. Serum 25-hydroxyvitamin D concentrations and prevalence estimates of hypovitaminosis D in the U.S. population based on assay-adjusted data. *J Nutr.* 2012;142(3):498-507.

Table 1. Baseline clinical characteristics of African-American breast cancer survivor study participants stratified by serum 25(OH)D cut-points proposed by the Endocrine Society and the Institute of Medicine (N=244)

	Endocrine Society[21]			Institute of Medicine[20]		
Variable[a]	**Sufficient 25(OH) D** ≥ 30 ng/ml (≥ 75 nmol/L)	**Insufficient 25(OH) D** < 30 ng/ml (< 75 nmol/L)	**P value[b]**	**Sufficient 25(OH) D** ≥ 20 ng/ml (≥ 50 nmol/L)	**Insufficient 25(OH) D** <20 ng/ml (< 50 nmol/L)	**P value[c]**
N	47	197		138	106	
Age [years (SD)]	61.3 (8.5)	56.5 (10.2)	**0.003**	58.4 (10.1)	56.1 (9.9)	0.077
Time since diagnosis [years (SD)]	7.7 (5.7)	6.9 (5.2)	0.376	6.9 (5.9)	7.3 (6.3)	0.475
Age at diagnosis [years (SD)]	53.4 (10.0)	49.6 (9.9)	**0.020**	51.5 (10.5)	48.8 (9.0)	**0.037**
Self-report breast cancer stage (n)			0.135			**0.001**

Stage I (%)	19	66		47	38	
Stage II (%)	20	78		66	32	
Stage III (%)	3	36		13	26	
Unsure	5	17		12	10	
Co-morbid conditions (n)						
Diabetes	17	39	**0.017**	34	22	0.475
High Cholesterol	20	72	0.445	54	38	0.600
Hypertension	37	107	**0.002**	90	54	**0.025**
Current Smoker (n)[d]	5	14	0.375	9	10	0.419
Currently taking vitamin D supplements (n)[e]	35	97	**<0.001**	97	35	**<0.001**
Education level (n)			0.438			0.823
High school or less	12	46		36	22	
Some college or Associate's degree	16	77		50	43	

College graduate or graduate degree	19	74		52	41	
Employment (n)			**0.004**			0.102
Full-time	21	66		51	36	
Part-time	1	26		16	11	
Retired	19	44		40	23	
Disabled/unable to work	2	32		12	22	
Other	4	29		19	14	
Insurance (n)			**0.035**			0.403
None	1	8		6	3	
Public	3	48		26	25	
Medicare	11	48		33	26	
HMO/PPO	32	91		73	50	
Other	0	2		0	2	
Current menopausal status			0.148			0.326
Pre-menopausal (n)	3	28		15	16	

Post-menopausal (n)	44	169		123	90	
Received chemotherapy for breast cancer (n)[d]	33	142	0.603	99	76	0.795
Received radiation therapy for breast cancer (n) [d]	36	153	0.640	102	87	0.204
Current endocrine therapy for breast cancer (n) [d]	13	58	0.716	46	25	0.071

a Data are presented as mean ± standard deviation (SD) or n.

b P value reflects comparisons made for > 30 vs. ≤ 30 ng/ml (or > 75 vs. ≤ 75 nmol/L) with bold values signifying statistical significance.

c P value reflects comparisons made for > 20 vs. ≤ 20 ng/ml (or > 50 vs. ≤ 50 nmol/L) with bold values signifying statistical significance.

d Data missing on 25 participants for current smoker and on 5 participants for breast cancer related therapies.

e Numbers reflect 132 women who reported supplemental vitamin D consumption.

Table 2. Body composition, dietary intake and sun exposure among African-American breast cancer survivors stratified by serum 25(OH)D cut-points proposed by the Endocrine Society and the Institute of Medicine (N=244)

	Endocrine Society[21]			Institute of Medicine[20]		
Variable[ag]	**Sufficient 25(OH)D** ≥ 30 ng/ml (≥ 75 nmol/L)	**Insufficient 25(OH)D** < 30 ng/ml (< 75 nmol/L)	**P value[b]**	**Sufficient 25(OH)D** ≥ 20 ng/ml (≥ 50 nmol/L)	**Insufficient 25(OH)D** <20 ng/ml (< 50 nmol/L)	**P value[b]**
N	47	197		138	106	
Body Weight (kg)	95.6 (15.9)	96.2 (18.8)	0.859	94.5 (17.1)	98.0 (19.5)	0.141
Height (cm)	161.9 (5.8)	163.1 (6.5)	0.247	162.6 (6.0)	163.1 (6.8)	0.527
Body mass index[b] (kg/m^2)	36.5 (5.9)	36.1 (6.3)	0.674	35.7 (6.0)	36.7 (6.5)	0.221
Overweight (n)	3	24	0.162	15	12	0.510
Class 1 Obese (n)	20	79		61	38	

Class 2 Obese (n)	17	63		35	28	
Class 3 Obese (n)	7	55		27	28	
Waist circumference (cm)	112.4 (12.5)	113.7 (15.9)	0.589	112.4 (14.1)	114.8 (16.6)	0.212
Hip circumference (cm)	121.0 (11.3)	120.6 (13.9)	0.870	120.0 (12.9)	121.6 (14.1)	0.367
Waist to hip ratio	0.93 (0.07)	0.94 (0.09)	0.325	0.93 (0.08)	0.95 (0.09)	0.502
DXA Total fat mass (kg)	44.6 (10.6)	44.7 (13.0)	0.994	43.5 (11.9)	46.2 (13.3)	0.092
DXA Body fat (%)	46.9 (3.90)	46.2 (5.20)	0.411	45.8 (5.0)	46.9 (4.7)	0.094
DXA Visceral fat mass (kg)	1.44 (0.67)	1.45 (0.70)	0.925	1.39 (0.67)	1.53 (0.72)	0.120
DXA Android fat mass (kg)	4.01 (1.23)	4.12 (1.50)	0.638	3.93 (1.36)	4.30 (1.51)	**0.049**

DXA Gynoid fat mass (kg)	7.56 (2.14)	7.54 (2.54)	0.978	7.33 (2.36)	7.83 (2.57)	0.120
DXA Leg fat mass (kg)	16.57 (4.84)	16.109 (5.75)	0.574	15.83 (5.29)	16.68 (5.93)	0.248
DXA Total lean mass (kg)	47.22 (5.58)	47.99 (6.90)	0.473	47.56 (6.34)	48.20 (7.06)	0.461
DXA Appendicular lean height (kg/m^2)	8.74 (1.15)	8.82 (1.28)	0.715	8.76 (1.17)	8.87 (1.36)	0.523
FFQ Energy intake (kcals/d)[e]	1769 (862)	2091 (1152)	0.094	1769 (813)	2339 (1342)	**<0.001**
FFQ Dietary vitamin D intake (IU/d)[e]	102 (80)	116 (100)	0.413	97 (67)	135 (129)	**0.01**
FFQ Supplement vitamin D intake (IU/d)[ef]	352 (194)	317 (158)	0.296	342 (175)	282 (140)	0.073

Daily summer sun exposure (hrs)	2.4 (1.6)	2.5 (1.7)	0.769	2.5 (1.6)	2.5 (1.7)	0.975
Self-reported skin color			**<0.001**			0.513
Fair	3	8		7	4	
Olive	3	7		6	4	
Light brown	20	84		61	43	
Dark brown	14	93		55	52	
Very dark	7	5		9	3	

a Data are presented as mean ± standard deviation (SD) or n.

b BMI (kg/m^2) cut-points defined as: overweight BMI 25.0-29.9; Class 1 obese BMI 30.0-34.9; Class 2 obese BMI 35.0-39.9; Class 3 obese BMI ≥ 40.0.[15]

c P value reflects comparisons made for > 30 vs. ≤ 30 ng/dl (or > 75 vs. ≤ 75 nmol/L) with bold values signifying statistical significance.

d P value reflects comparisons made for > 20 vs. ≤ 20 ng/dl (or > 50 vs. ≤ 50 nmol/L) with bold values signifying statistical significance.

e Due to changes in FFQ version, only dietary data from cohorts 2-8 were evaluable (n=219).

f These calculations reflect the 132 participants who reported intakes of supplemental vitamin D.

g Abbreviations used: BMI= Body mass index, FFQ=Food Frequency Questionnaire, DXA=Dual energy x-ray absorptiometry