



Original Research

Body Composition, Metabolism, and Inflammation in Breast Cancer Survivors and Healthy Age-matched Controls: A Cross-Sectional Analysis

TAKUDZWA A. MADZIMA[‡] and CAROLINE D. DEATERLY*

Department of Exercise Science, Energy Metabolism and Body Composition Laboratory, Elon University, Elon, NC, USA

*Denotes undergraduate student author, [‡]Denotes professional author

ABSTRACT

International Journal of Exercise Science 13(3): 1108-1119, 2020. Breast cancer survivors (BCS) experience treatment induced alterations in body composition including the loss of bone mineral density (BMD) and lean soft tissue (LST). These changes can affect the metabolism and the systemic inflammatory environment of BCS. Objective: To evaluate the differences in body composition, resting energy expenditure (REE), and inflammation in BCS and age-matched women without a prior cancer diagnosis (control). Methods: Seventeen post-menopausal BCS (stages 0-III; age: 59 ± 9 years) and 18 (59 ± 6 years) controls had their total body and regional (lumbar spine, femur, and forearm) BMD, LST and fat mass measured via DXA. REE was assessed via 35 minutes of indirect calorimetry. Serum concentrations of human C-reactive protein (CRP) were measured via ELISA to assess inflammation. Data were analyzed via ANOVAs. Results: There were no significant differences between BCS and controls in body composition, metabolic measures and CRP. However, when REE was adjusted for LST, the BCS had a significantly greater REE when compared to the controls ($p = 0.015$). Discussion: Our findings suggest that BCS that were on average five years into survivorship appear to have similar body composition, and CRP as age-matched women without a prior cancer diagnosis, but significantly different relative REE.

KEY WORDS: Metabolism, osteosarcopenic obesity, cancer survivorship, lean soft tissue, C-reactive protein.

INTRODUCTION

Breast cancer is the most prevalent cancer in American women, with an estimated 268,600 new cases and 41,760 deaths projected in 2019 (42). Although mortality rates have been declining over the decades (42) as a result of increased early detection and improvements in treatment, breast cancer survivors (BCS) are often left to live with treatment related side effects (18,37,41). Among these side effects, include the acceleration of the negative age-related changes in body composition, specifically the loss of both bone mineral density (BMD) and lean soft tissue (LST) with the concurrent increase in fat mass (41).

Cancer treatments directly and indirectly increase bone loss and thus the progression to osteopenia and/or osteoporosis through various physiologic mechanisms (31). Bone turnover

increases in favor of bone resorption as adjuvant chemotherapy agents directly interrupt the normal bone remodeling process (19,31). Cancer therapies also affect bone through the reduction in circulating estrogen, the hormone that plays a role in increasing bone formation through increasing osteoblast activity (31). Chemotherapy indirectly reduces estrogen levels by inducing permanent ovarian failure in 50-85% of breast cancer patients (6,20). Whereas, adjuvant hormone suppression therapy inhibits estrogen production in adipose tissue through aromatase inhibitors (34,36). This creates an imbalance between osteoblastic and osteoclastic activity that results in an overall increase in the rate of bone turnover (35).

Decrements in LST during breast cancer, occurs as a result of the catabolic nature of the cancer itself, as well as a result of the therapy (18,37,41). Several treatment modalities can influence muscle protein synthesis and ultimately muscle mass, leading to losses of the LST compartment (mainly composed of muscle mass) (37). Accelerated body composition changes also occur due to metabolic alterations (reduced appetite, anorexia, hypercatabolism) induced during tumor-bearing period (33). Additionally, in cancer patients tumor induced increases in systemic inflammation can inhibit the pathways for muscle protein synthesis and promote muscle protein breakdown (15). Further, fatigue as a side effect of chemotherapy decreases physical activity levels in women undergoing treatment (13), thereby decreasing the mechanical stimuli that is needed to maintain skeletal muscle mass. The reduced physical activity levels also promotes the accretion of fat mass in women diagnosed with breast cancer due to a reduction in physical activity and energy expenditure, thus creating an imbalance between energy intake and expenditure (18,41). Elevated levels of body fat increase the levels of circulating inflammatory markers, further exacerbating the loss of LST (7). All these factors ultimately create a vicious cycle of alterations in all three body composition compartments.

The cancer and/or treatment-related alterations in body composition may lead to phenotypes known as sarcopenia (low muscle/lean soft tissue) and sarcopenic obesity (combined sarcopenia with excess body weight). Sarcopenia and sarcopenic obesity are prevalent and are predictors of poorer prognosis in breast cancer patients (38,39). Among 471 women with stages I-III breast cancer, sarcopenia was evident in 16% of the women, and was an independent predictor of shorter survival (48). The combined alterations in body composition has been more recently characterized as the multifactorial phenotype termed osteosarcopenic obesity (28).

Abnormal body composition may have an impact beyond cancer disease trajectory affecting survivorship. Consequences of decrements in LST include reductions in muscular strength (1,43) and alterations in metabolism (24) in BCS to a greater extent than that observed with normal aging. Changes in body composition and inflammation are also likely to affect resting energy expenditure (REE) as a 3% decline in REE was reported in patients receiving adjuvant chemotherapy, which remained reduced 3 months after completion of treatment (24). Sustained decrements in REE creates an imbalance between energy intake and expenditure that can further persist long-term weight gain in BCS (24).

Despite an understanding of the mechanisms contributing to the accelerated age-related changes in body composition in early BCS it is unclear whether these differences persist several years into survival. Similarly, it is yet to be determined whether associated factors such as

increased inflammation and depressed REE exist in BCS several years posttreatment. A reasonable follow-up question from the research conducted, is whether the changes in body composition, inflammation, and metabolism in BCS that are several years posttreatment is attenuated and resembles that of normal aging. Therefore, the aim of this cross-sectional study was to compare the differences in body composition and the prevalence of osteosarcopenic obesity between BCS and age-matched women without a prior cancer diagnosis (control). A secondary aim of the study was to evaluate the differences in the metabolic and inflammatory profile between BCS and control relative to the differences in body composition.

METHODS

Participants

Seventeen post-menopausal female BCS (age: 59 ± 9 years; treated for stages 0-III) and 18 age-matched women (age: 59 ± 6 years) without a prior cancer diagnosis (control) were recruited via flyers posted in the community and recruit through local breast cancer support groups, local churches, groups on campus, and community groups. The BCS were at least three months post primary (surgery) and adjuvant treatment (chemotherapy and/or radiation). Women currently on hormone suppressant therapy were included as these therapies are often prescribed for 10 years post diagnosis. Women diagnosed with stage IV breast cancer or who had active cancer were excluded. The rationale for excluding women with stage IV breast cancer was that these women would likely to have the cancer metastasized to the bone and our study aimed to compare BCS without metastasized cancer to controls. Participants were excluded if they had any physical limitations that would prevent participation in exercise testing, as well as if they had hypo or hyperthyroidism, uncontrolled hypertension, uncontrolled diabetes, heart disease, kidney disease, or were taking medications known to influence metabolism. This research was carried out fully in accordance to the ethical standards of the International Journal of Exercise Science (32). The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human participants were approved by the University Institutional Review Board. Written participant informed consent and physician consent were obtained before participation in the study.

Protocol

Eligible participants were scheduled for two testing visits, each separated by one week. During the first visit, participants completed a demographics and medical history questionnaire. Participants returned to the laboratory after an 8 hour fast between 6:00 AM and 9:00 AM for their second testing visit, which included blood collection and assessments of resting energy expenditure and body composition. The laboratory testing visits were separated by at least seven days.

Prior to testing, participants were asked to refrain from exercise, caffeine, and alcohol for 24 hours and reported to the laboratory between 0600 and 0900 hours. Fasting (>8 hours) venous blood samples in the amount of 20 milliliters were collected from the antecubital space to measure serum levels of human C-reactive protein (CRP) as measures of systemic inflammation. Due to the scope of this study, this biomarker was chosen in order to understand the possible relationships between diet, body composition and inflammation in breast cancer survivors as

well as compare these variables to healthy age-matched women. Serum CRP levels greater than 3.0 mg/L was used to determine the presence of low grade chronic inflammation in the present study (21). Analysis of serum CRP was conducted at the conclusion of the study via one enzyme-linked immunosorbent assay (R&D Systems®). The serum samples were run in duplicate and the intra-assay coefficient of variation (CV) was 19.4%. Samples with a CV >20% were excluded from analysis.

Following the blood draw, the participants had their REE, and non-protein respiratory quotient (RQ) measured via indirect calorimetry using the ventilated hood technique (ParvoMedics TrueOne 2400, Sandy, Utah). The participants were asked to lay supine on a padded table in a dark, quiet and climate-controlled room for a total of 1 hour and 5 minutes, which comprised of 30 minutes at rest, then 35 minutes of continuous gas exchange measurements with the ventilated hood covering the head and torso. The final 30 minutes of gas exchange measurements were used to determine oxygen consumption (VO_2 ; ml/kg/min), predicted 24 hour REE (kcal/day) and REE adjusted for LST (kcal/day/kg) to use for analysis.

Upon completion of the REE assessment, height and weight were measured using stadiometer and scale, respectively (Seca Corporation; Hanover, MD) to calculate the body mass index (BMI; kg/m²). Body composition was measured via dual energy X-ray absorptiometry (DXA; Prodigy Advance, GE Medical Systems; Madison, WI). The BMD of the lumbar spine (L1-L4), right and left femoral neck, and right and left forearm were measured and analyzed by the same licensed technician according to manufacturer's guidelines and specifications. In addition, total body and regional LST, fat mass, and percent body fat were measured via DXA. The appendicular skeletal muscle mass index (arm + leg LST) adjusted by height (ASMI; kg/m²) was calculated to determine the presence of sarcopenia. In the present study, the presence of osteosarcopenic obesity was determined according the criteria defined by Ilich et al. (28) as having a T-score < -1.0 standard deviations below the mean of young adult reference values at the lumbar, or femoral neck. Sarcopenia was defined as having an ASMI of <5.45 kg/m² (5). Obesity was defined as having a DXA derived fat mass >32%.

Statistical Analysis

Descriptive statistics including mean and standard deviation were determined for all variables. Dependent variables were analyzed via a one-way analysis of variance (ANOVA). When Levene's test for equality of variances was violated, the Welch ANOVA was used to compare group differences. All significance was accepted at $p < 0.05$. Statistical Analysis was done using the SPSS version 24 statistical software (IBM®, Armonk, NY).

RESULTS

A comparison of participant descriptive data between BCS and controls as well as the cancer history of BCS are displayed in Table 1. There were no significant differences between BCS and controls in all variables except for menopausal age. The BCS entered menopause at a significantly younger age than the controls ($p = 0.042$). Thirty-three of the participants were Caucasian and two were Asian.

Table 1. Descriptive characteristics of participants.

	BCS (n = 17)	Controls (n = 18)
Age (years)	59±9	59±6
Menopause age (years)*	47±4	50±4
BMI (kg/m ²)	26.4±5.1	25.3±3.8
Time since diagnosis (months)	76.4±17.8	.
Time since primary treatment completed (months)	75.7±17.8	.
Time since completion of hormone therapy (months)	37.8±22.9	.
Stage 0 (%)	6.3%	.
Stage I (%)	62.5%	.
Stage II (%)	12.5%	.
Stage III (%)	18.8%	.

Values are mean ± SD; BCS = breast cancer survivors; BMI= body mass index; * *p* < 0.05 indicates statistically significant difference between BCS and controls.

Table 2 presents the measures of body composition. Lean soft tissue, fat mass, ASMI and total body fat did not differ between the groups. Similarly, there were no significant differences in any BMD measures. Table 3 presents a comparison of the criteria for osteosarcopenic obesity. Based on these criteria, only one participant, a BCS was classified as having osteosarcopenic obesity.

Table 2. Comparison of body composition measures between BCS and controls.

	BCS (n = 17)	Controls (n = 18)	P-value
LST (kg)	38.1±4.5	38.4±3.9	0.817
Fat Mass (kg)	28.3±9.4	26.6±7.6	0.568
ASMI (kg/m ²)	6.22±0.9	6.04±0.9	0.479
Total Body Fat (%)	41.6±7.1	39.8±6.2	0.442
Lumbar BMD (g/m ²)	1.097±0.0186	1.064±0.0185	0.607
Left Femoral Neck (g/m ²) [‡]	0.851±0.080	0.878±0.091	0.367
Right Femoral Neck (g/m ²) [‡]	0.807±0.211	0.859±0.083	0.340
Left Femur (g/m ²) [‡]	0.924±0.091	0.916±0.093	0.815
Right Femur (g/m ²) [‡]	0.928±0.099	0.906±0.097	0.507
Left Radius Total (g/m ²)	0.592±0.087	0.607±0.043	0.538
Right Radius Total (g/m ²)	0.606±0.089	0.603±0.055	0.882

Values are mean ± SD; BCS = breast cancer survivors; LST = lean soft tissue, ASMI = appendicular skeletal mass index; BMD = bone mineral density; [‡] n = 16 for BCS group because one participant had dual hip replacement.

Table 3. Prevalence of osteosarcopenic obesity criteria between BCS and controls.

	BCS (n = 17)	Controls (n = 18)
Low BMD Lumbar Spine (L1-L4) [‡]	7 (41.2)	3 (16.7)
Low BMD Left Femoral Neck [‡]	12 (70.6)	9 (50.0)
Low BMD Right Femoral Neck [‡]	13 (76.5)	12 (66.7)
Sarcopenia	2 (11.8)	1 (5.6)
Obesity	16 (94.1)	17 (94.4)
Sarcopenic Obesity	1 (5.9)	0 (0.0)
Osteosarcopenic Obesity	1 (5.9)	0 (0.0)

Values are n (% of sample); BCS = breast cancer survivors; [‡] Low BMD classified as T-score < -1 SD

A comparison of the metabolic measures between BCS and controls are presented in table 4. One participant from each group did not complete the metabolic assessments due to feelings of claustrophobia when laying under the ventilated hood. There were no significant differences between BCS and controls for resting VO₂, predicted REE, and respiratory quotient. However, when REE was adjusted for LST, the BCS had a significantly greater REE when compared to the controls ($p = 0.015$).

Table 4. Comparison of metabolic and inflammatory measures between BCS and controls.

	BCS ($n = 17$)	Controls ($n = 18$)	P-value
Metabolism			
VO ₂ (ml/kg/min)	2.94 ± 0.39	2.87 ± 0.77	0.758
REE (kcal/day)	1381 ± 191	1270 ± 184	0.099
REE adjusted for LST (kcal/day/kg)	36.1 ± 2.22	33.0 ± 4.3	0.015
Respiratory Quotient	0.73 ± 0.04	0.75 ± 0.05	0.116
Inflammation			
CRP (mg/L) ‡	3.74 ± 1.45	3.34 ± 1.64	0.263

Values are mean ± SD; BCS = breast cancer survivors; VO₂ = oxygen consumption; REE = resting energy expenditure; LST = lean soft tissue; CRP = C-reactive protein; ‡ $n = 13$ for BCS and $n = 9$ for controls. * $p < 0.05$, significant difference between BCS and controls.

Table 4 also presents the serum levels of the inflammatory marker CRP. Three participants from each group had unsuccessful blood draws and thus were not able to have CRP measured. In addition, one BCS and four controls had CVs greater than 20% and were thus excluded from analysis. Therefore, thirteen BCS and nine controls had CRP levels analyzed. There were no significant differences in CRP levels between BCS and controls. However, more BCS ($n = 9$) did have CRP levels above 3.0 mg/L than controls ($n = 3$).

DISCUSSION

The main findings of our present study are that BCS that are 75.7 ± 17.8 months (6.31 ± 1.5 years) after completion of primary treatment have greater relative REE compared to controls. However, the BCS in our study had similar body composition, absolute REE, RQ, and circulating CRP levels. Despite BCS having menopause at a significantly younger age, the BMD at several skeletal sites and the prevalence of osteoporosis, sarcopenia, and osteosarcopenic obesity also did not differ from controls.

Our findings of similar body composition measures (LST, fat mass, ASMI, total body fat and BMD) between BCS and controls is in agreement to previous studies investigating BCS that are on average more than 5 years posttreatment (3,43). In contrast to our findings, Twiss et al. (46) observed that more BCS had low BMD in the lumbar spine when compared to the femur. In addition, the work from Simonavice et al. (43) found that total forearm BMD was 11% lower in BCS when compared to controls, and the difference in forearm BMD was confirmed by a more recent study by Artese et al. (3). However, our findings of no differences in lumbar spine and femur BMD are consistent with previous findings (3,12,43). Whereas, Ferreira Poloni et al. (17) observed that osteopenia and osteoporosis in the femoral neck was more prevalent in BCS (14.5 ± 8.5 years post-menopause) when compared to controls with a similar time since menopause. Further, across all skeletal sites, low bone mass (osteopenia or osteoporosis) was present in 77%

of BCS compared to 74.5% in controls (17). Despite the lack of significant differences in BMD between BCS and controls in the present study, more BCS had low BMD (T-score <-1.0) at the lumbar (41.2 vs. 16.7%) and left femoral neck (70.6 vs. 50.0%). Although our sample is small, the prevalence of low BMD in our study at the lumbar spine (41.2 vs. 45.7%) is similar that observed in 70 BCS (53.2 ± 5.9 years) that were also ~5 years post-diagnosis (11). However when comparing BMD at the femoral neck, our BCS had a greater prevalence of low BMD (76.5 vs. 28.6%) than the BCS in the study by Conde et al. (11).

These differences between our findings and those of Conde et al. (11) may be due to our BCS being slightly older (59 ± 9 vs. 53 ± 6 years), despite more of our BCS being diagnosed at an earlier stage (stage 0 or I: 68.8 vs. 28.5%) and having a slightly greater time since diagnosis (76.4 ± 17.8 vs. 65.2 ± 55.1 months). Although it has been reported that age- and hormonal-related decrements in BMD cause greater losses of BMD at the lumbar spine than the femur (10,53), not all studies agree (47,50). In fact, there are several factors that have been associated with the site-specific BMD changes including BMI (47,50,52), LST (26), postmenopausal status (29) and a longer time since diagnosis (11,53). Despite the lack of group differences, our findings highlight the prevalence of low BMD in postmenopausal women regardless of cancer diagnosis that is consistent with existing literature. Although several exercise and/or nutritional interventions have been conducted to address low BMD in BCS (45,52) and cancer-free postmenopausal women (2,27,49), more work is needed in this area. Particularly since low BMD is associated with up to a 4.0 fold increase in the rate of fractures in postmenopausal women (45). Interestingly, only one BCS had sarcopenic obesity in our study. This low prevalence, although positive, may be due to our small sample size, with the majority of our BCS being greater than 5 years post treatment and being primarily diagnosed with stage I (62%). Thus, they may not experience the decrements that recent survivors and more advanced stage BCS may experience.

Although not all BCS are overweight and obese, it has been consistently reported that BCS experience significant weight gain (14,18). This may lead to some metabolic disturbances related to increased adiposity including insulin resistance, dyslipidemia, and chronic inflammation (16,31). The present study sought to determine whether BCS several years after diagnosis had greater metabolic disturbances as determined by absolute and relative REE as well as CRP to measure inflammatory status. Absolute REE and inflammation were similar between BCS and controls. However, when REE was adjusted for LST, the BCS had a significantly greater REE than the controls. The majority of BCS (94.1%) and controls (94.4%) in the present study were classified as obese based on body composition (body fat > 32%), despite mean BMI values that only classified both the BCS and controls as overweight (26.4 ± 5.1 and 25.3 ± 3.8 kg/m²). Data surrounding changes in REE within the cancer population are conflicting (23,24,26). Campbell et al. (8) did not observe a change in REE in 10 breast cancer patients undergoing adjuvant chemotherapy, despite an increase in fat mass. Other studies (9,24,25) have observed increases in REE in cancer populations primarily during the tumor-bearing period. These observed increases in REE have led to up to 73% of cancer patients being reported to experience some degree of accelerated body composition changes such as weight loss (muscle and fat) during their disease course (33,40).

Further, these changes in REE occur primarily in cancers of metabolically active organs (e.g. liver, pancreatic) (33). However, during and after treatment REE may decrease and remain depressed in the months following completion of primary treatment (24). A study by Guinan et al. (22) stratified 69 BCS (age: 53.4 ± 9.39 years) that were 3.1 ± 1.0 years post diagnosis into four groups based on abdominal obesity (waist circumference) and insulin resistance and compared both the absolute REE and REE adjusted by fat-free mass among the BCS. The BCS with the worst metabolic profile (waist > 88cm and insulin resistant) had significantly greater REE and CRP than the BCS with healthier metabolic profiles (normal waist circumference and/or absence of insulin resistance). Interestingly, objectively measured habitual physical activity levels were not associated with REE in the cohort of BCS investigated by Guinan et al. (22). The average absolute REE of the group with the worst metabolic health (waist > 88cm and insulin resistant) was greater than our BCS (6191 ± 959 vs. 5776 ± 798 kJ/day), whereas the LST adjusted REE was lower compared to the BCS in the present study (122 ± 10.7 vs. 151 ± 9.31 kJ/day/kg). Similarly in a large study by Cao et al. (9), REE was not different between newly diagnosed cancer patients from various cancer types and healthy controls. However, when REE was adjusted to fat-free mass, the cancer patients had significantly higher REE regardless of age and gender (9). Thus, the findings of our small pilot study suggest that BCS > 5 years posttreatment may have unclear or similar metabolic function as age-matched women without a prior cancer diagnosis. It is possible that a tumor developed in breast tissue may not result in a significant metabolic burden as compared to tumors in more metabolically active organs (e.g. liver, pancreas) (9).

The present study also measured the acute-phase reactant CRP to determine the inflammatory status of our participants. Similarities in the body composition of our participants may explain the lack of differences in serum CRP between the BCS and controls. Despite the lack of group differences, more BCS (53%) had chronic low-grade inflammation (CRP > 3.0 mg/L) compared to controls (16%). The average CRP values of the BCS (3.74 ± 1.45 mg/L) and controls (3.34 ± 1.64 mg/L) in the present study were greater than the BCS in the normal to moderate weight, non-insulin resistant groups (1.53-2.09 mg/L) but less than the obese, insulin resistant BCS (4.98 ± 3.46 mg/L) in the study by Guinan et al. (22). Therefore, it is unclear if the interaction between body composition and metabolic profiles differs in BCS several years posttreatment with that of age-matched women without a prior cancer diagnosis. Nevertheless, evidence suggests a significant association between elevated CRP with increased risk of and reduced survival from breast cancer (4). Further, survivors in a chronic state of inflammation have a higher chance of cancer recurrence and metabolic disturbances (4). Thus, regardless of cancer diagnosis, interventions to reduce chronic inflammation are necessary for postmenopausal women.

It is important to note that the BCS in the present study were primarily diagnosed with stage I breast cancer (62%) and 59% of our BCS were treated with chemotherapy. In addition, we determined that only 2 BCS in our sample had low muscle mass (sarcopenia). Therefore our findings suggest that the amount of LST plays a role in the comparable metabolism between the BCS and postmenopausal women in our study. This highlights the importance of maintaining and/or regaining LST in BCS. Whether metabolism differs in BCS that had a more advanced stage diagnosis still needs to be determined.

The present study did have some limitations. First, this cross-sectional study had a relatively small sample size of BCS and controls, therefore future studies including larger sample sizes are needed to confirm our findings. Secondly, we did not collect physical activity and dietary data that may explain the similarities between BCS and controls. Lastly, our study contained a heterogeneous sample of BCS that differed in their diagnosis, time since diagnosis, and type of treatment which may have affected the extent of side effects experienced. Therefore, differences between BCS and controls in our main outcome measures may have been attenuated.

In conclusion, our small study shows BCS that are on average several years post-completion of primary treatment have similar body composition, absolute REE, RQ, and circulating CRP levels to age-matched women without a prior cancer diagnosis. However, when REE was adjusted for LST, the BCS had greater relative REE compared to controls. More research studies with larger sample sizes of BCS are needed to determine if the accelerated treatment related decrements in these health outcomes extend far into the survival years. In addition, larger studies may determine if the similar health outcomes in BCS are in fact a result of more proactive and health conscious activities in the years after completion of treatment.

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