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Metabolic Syndrome and Elevated C-Reactive Protein in Breast Cancer Survivors on Adjuvant Hormone Therapy

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Abstract

Aims: As the efficacy of treatment for breast cancer has improved, particularly with the use of antiestrogenic therapies, there is an increasing population of long-term breast cancer survivors who seeks care with unique health issues. These patients may be at increased risk for cardiovascular disease (CVD) resulting from excess adiposity and treatment effects. Metabolic syndrome (MetS) and elevated C-reactive protein (CRP), two predictors of CVD, have not been fully evaluated in overweight breast cancer survivors on hormone-modulating agents.

Methods: Anthropometric measures, including weight, height, waist and hip circumferences; clinical laboratory assessments, including lipids, glucose, glycoslyated hemoglobin (HbA1c), insulin, and high sensitivity CRP; and body composition and blood pressure (BP) were collected from overweight breast cancer survivors ($n = 42$). Select measures were used to derive MetS using the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) diagnostic criteria.

Results: Participants had a mean body weight of 83.8 kg and body mass index (BMI) of 31.4 kg/m^2. Mean fasting glucose (98 ± 12.9 mg/dL), HbA1c (6.0 ± 0.5 mg/dL), cholesterol (199 ± 33.7 mg/dL), and insulin (16 ± 13.2 mg/dL) were all at the upper end of the normal range. MetS was diagnosed in 54.8% of overweight postmenopausal breast cancer survivors. CRP was moderately or severely elevated in 90.5% of the population (mean of 5.1 ± 5.3 mg/dL).

Conclusions: In our sample, overweight breast cancer survivors commonly have MetS and elevated CRP that place them at increased risk for cardiovascular and other metabolic diseases. If replicated in a larger sample, this warrants close medical monitoring to prevent and reduce morbidity and mortality unrelated to breast cancer.

Introduction

High adiposity levels and low-grade chronic inflammation are suspected risk factors for recurrent disease among women previously treated for breast cancer.[1] Although inconsistent across studies, being obese at the time of a breast cancer diagnosis[2–4] or increasing weight postdiagnosis has been associated with an elevated risk of recurrence.[5] Chemotherapy and hormonal therapies used to treat breast cancer are associated with sarcopenic weight gain in this population, and the increase in body fat combined with a loss of lean mass may be particularly detrimental in terms of future metabolic disease.[6,7]

Overweight or obesity, particularly when characterized by central adiposity, has been associated with elevated levels of proinflammatory factors, as well as the subsequent development of metabolic syndrome (MetS), a clustering of metabolic disturbances that increase risk for type 2 diabetes and cardiovascular disease (CVD).[8,9] Elevations in systemic inflammatory markers[10,11] and the presence of MetS[12] have been associated with reduced survival for cancers and breast cancers, respectively, although the number of studies is limited and results are not consistent across all studies.[13] Further, chronic inflammation and MetS increase cardiovascular risk among survivors,[14] contributing to competing causes of death in a population of women under significant postcancer medical surveillance.

Evaluating the clinical status and chronic disease risk factors of the overweight breast cancer survivor is complicated by the common, long duration (>10 years) use of selective estrogen receptor modulators (SERMs) (e.g., tamoxifen, raloxifene), or aromatase inhibitors (AIs) (e.g., letrozole, anastrozole, exemestane), which may modulate select indicators of risk. Tamoxifen has been associated with higher visceral

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adiposity among women treated for breast cancer.[15] In placebo-controlled analyses, however, tamoxifen use has been associated with lower atherosclerotic and myocardial infarct (MI) risk,[16,17] possibly through reductions in C-reactive protein (CRP), fibrinogen, and total and low-density lipoproteins (LDL),[16] mediated by weak estrogenic effects on lipoprotein lipase.[18,19] More recently, the displacement of SERMS with AIs in the treatment of hormone-positive tumors has raised concerns about agent-specific potential to decrease high-density lipoprotein (HDL) levels[20] and the possible impact on cardiovascular risk, particularly for older breast cancer survivors, who are more likely to die from CVD than breast cancer,[21–23] and for women with preexisting cardiovascular risk factors.[24]

The purpose of this analysis was to evaluate and report, using baseline data from a weight control diet intervention study of overweight breast cancer survivors, the presence of abnormalities in two strong predictors of CVD risk, MetS and elevations in high sensitivity CRP (hsCRP), in this population. These and related individual metabolic risk factors appear to be associated with increased risk for a wide spectrum of comorbidities, including cancer recurrences, diabetes, and CVD, in this growing segment of healthcare consumers. A better understanding of the commonality of MetS, presentation of metabolic abnormalities, and elevations in CRP in breast cancer survivors will support the earlier diagnosis and management of metabolic disturbances.

Materials and Methods

Study participants

Breast cancer survivors with stage I or II invasive disease were recruited from clinics of the Arizona Cancer Center, University of Arizona. Eligibility criteria included women who were 6–72 months from surgery or completion of radiation or chemotherapy (with the exception of estrogen modulators), body mass index (BMI) $>25\,kg/m^2$, no significant body weight loss in the 12 months prior to study enrollment, and no history of chronic disease, including diabetes. All subjects were currently receiving some form of hormone suppression therapy with SERMs or AIs. All subjects provided written informed consent and completed the consenting process per institutional guidelines at the University of Arizona.

Body measures and resting energy expenditure

Body weight, height, and waist and hip circumferences were measured at the research clinic using standardized protocols,[25] with BMI (kg/m^2) and waist/hip ratio determined. In addition, women were asked to self-report their adult weight history (weight at age 18, 1 year ago, 5 years ago, and at the time of breast cancer diagnosis) using standard weight history questionnaire items from the Women's Healthy Eating and Living (WHEL) Study Lifestyle Questionnaire.[26] Body composition was assessed by dual x-ray absorptiometry (DXA). Whole body DXA scans were collected to estimate whole body fat, lean soft tissue, bone mass, appendicular (arm plus leg) skeletal muscle, and trunk fat using standard Lunar DPX-IQ whole body densitometer procedures and protocols for positioning and data acquisition protocols, which were executed by certified radiation technicians. Resting energy expenditure was measured by the respiratory gas exchange method using MedGem portable indirect calorimeter[27] under standardized conditions.

Dietary intake and physical activity assessment

Dietary intake was assessed using the validated Arizona Food Frequency Questionnaire (AFFQ), which has been validated for research use.[28] The AFFQ consists of a semiquantitative 159-item food frequency questionnaire, which asks respondents to report how often they usually consumed each particular food over the prior 12-month period. This instrument was used to estimate self-reported food intake patterns, energy, macronutrient intake (carbohydrate, protein, and fat), and micronutrient intake (vitamin, mineral, trace element, and electrolyte). The questionnaire was completed by the participant at the initial clinic visit and reviewed by the study coordinator for completeness. The Behavioral Measurements Shared Service of the Arizona Cancer Center provided the questionnaires, data scanning, and analysis for this project.

Physical activity was measured using the AAFQ. The AAFQ is in scannable format and provides output in metabolic equivalents (METs) per day, time per day at each activity level, time in load-bearing activities, time in social activities, and time in each major activity category. The MET estimations are derived from the Compendium of Physical Activity codes and MET intensities.[29] The questionnaire groups physical activity by leisure, recreational, household, and other activity categories and has been validated in 35 relatively sedentary women who completed the AAFQ prior to participating in an 8-day doubly labeled water protocol to measure total energy expenditure.[30] Using a predictive equation, total energy expenditure calculated from the AAFQ was highly correlated with doubly labeled water total energy expenditure ($p < 0.001$).

Clinical/biochemical outcome measures

Clinical laboratory measures included fasting glucose, insulin, and glycosylated hemoglobin (HbA1c), as well as lipids (total cholesterol, HDL, LDL, triglycerides). Additionally, thyroid function was assessed using thyroid-stimulating hormone (TSH) levels. A 2-hour oral glucose tolerance testing (OGTT) was performed as an additional measure of insulin resistance. Briefly, women were brought into the clinical laboratory in a fasting state, and the initial blood sample for glucose was drawn. Women were then given 75 g of oral glucose, and repeat blood sampling for glucose response was done at 30, 60, and 120 minutes. Inflammatory status was assessed using hsCRP. Fasting plasma samples were provided to the cancer center clinical laboratory where CRP levels were run on an automated turbidimetry analyzer with coefficient of variation (CV) of 1.8%–2.3%. Blood pressure (BP) measurements were collected at oncology care visits with the patient in a sitting position. These were single measures without standardization for meals, medications, or physical activity. To be classified as having MetS, patients had to have demonstrated the presence of at least three criteria for the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) definition of MetS[31]: triglycerides $\geq 150\,mg/dL$; waist circumference $>88\,cm$ (women); fasting glucose $\geq 100\,mg/dL$; systolic or diastolic BP ≥ 130 or 85 mm Hg, respectively; HDL cholesterol $<50\,mg/dL$.

Statistical analysis

Descriptive statistics (mean, median, range, % of population, and standard deviations [SD]) were calculated for demographic, clinical, dietary, anthropometric, and biomarker data for the 42 study participants. A variable containing the count of risk factors for MetS was created for each participant, and the mean with SD is reported. Additionally, a binary variable distinguished between women with three or more and women with less than three criteria. Percentages of women defined as having MetS were reported using this variable. Predictors of MetS were evaluated by backward multiple logistic regression, adjusting for age at study entry, time since cancer diagnosis, and 2-hour postload glucose level by OGTT. All statistical analyses were performed using SPSS v16.0 (SPSS Inc., Chicago, IL).

Results

The demographic and clinical characteristics of the study population are presented in Table 1. The majority of women enrolled were white, nonsmoking, employed, and well educated. Mean age was 55.9 years. Women were most commonly prescribed aromatase inhibitors (76.2%), whereas 23.8% were taking tamoxifen, a prescription pattern consistent with treatment practices at the time. Over half were on concurrent medications that could modulate metabolic indices, with nearly 24% receiving anticholesterol medications (statins) and 38.1% receiving antihypertensive medications.

The mean reported energy intake was 1951 Kcal/day—approximately 300 Kcals above daily energy requirements for weight maintenance in overweight older women reporting sedentary–light physical activity patterns (Table 2). The macronutrient composition of the average diet suggested the study population adhered to a relatively low-fat diet with a mean fat intake of 30.1% of total energy intake; mean dietary fiber intake was consistent with recommended intake levels.[32] Average resting energy expenditure was just over 1300 Kcals/day, and total daily energy expenditure averaged 2200 Kcals/day.

Anthropometric and body composition measures demonstrated a mean body weight and BMI of 83.8 ($\pm$ 12.4) kg and 31.4 ($\pm$ 4.2) kg/m^2, respectively (Table 3). Subjects also demonstrated high body fat (46.9% $\pm$ 5.4) and a propensity for high central adiposity as reflected in elevated trunk fat mass and waist/hip ratio above the norm of $<$0.85. In relation to adult weight history, the majority of subjects reported adult onset weight gain, with an average increase in body weight of 9.3 kg in the previous 5 years and a 25.6 kg average increase in body weight since early adulthood.

A diagnosis of MetS was demonstrated in 54.8% of the overweight breast cancer survivors using NCEP-ATP III criteria.[31] Specific mean and median biochemical measures for glucose-insulin-associated and lipid-related assessments are presented in Table 4. Waist circumference ($>$88 cm) was the most common criterion for MetS in our population (96%), with elevated systolic BP and low HDL levels being the next most common (65%). Statin therapy tended to protect patients from MetS, as 30% of patients on statins vs. 70% of those not receiving statins were found to meet MetS criteria (chi-square $p = 0.06$). There were no significant differences across hormone treatment groups (SERMS vs. AIs) for prevalence of MetS, although the small sample size limits interpretation of these analyses. The mean hsCRP level in our population was 5.1 mg/dL, significantly above the clinical norm of $<$1.0 mg/dL and higher than referent values from population studies and the Women's Heart and Health Study.[33]

Table 1. Characteristics of Overweight/Obese Breast Cancer Survivors ($N = 42$)

Characteristic	*Mean (SD) or* n *(%)*
Age, years	55.9 (9.4)
Range	38–77
Race/ethnicity	
Caucasian	34 (81%)
Other	8 (19%)
Tobacco use	
Never	25 (59.5%)
Current	4 (9.5%)
Past	13 (31%)
Partner status	
Married/cohabitating	31 (73.8%)
Single/divorced/widowed	11 (26.2%)
Education level	
High school or equivalent, or trade school	15 (35.7%)
College or postgraduate degree	23 (54.7%)
Other	4 (9.5%)
Employment status	
Full-time	22 (52.4%)
Part-time	3 (7.1%)
Retired	13 (31%)
Other	4 (9.5%)
Breast cancer diagnosis and treatment	
Stage at diagnosis[a]	
Stage 0	2 (4.8%)
Stage I	12 (28.6%)
Stage II	25 (59.5%)
Stage IIIA	2 (4.8%)
Time since diagnosis, months	44.8 (40.0)
Range	6.4–239.0
Age at diagnosis, years	53.0 (9.2)
Range	35–73
Chemotherapy (yes)	31 (73.8%)
Hormone-modulating therapy	
Tamoxifen use	10 (23.8%)
Aromatase inhibitor use	32 (76.2%)
Concurrent medications	
Antihypertensives	16 (38.1%)
Psychotrophic agents	22 (52.4%)
Anticholesterol agents	10 (23.8%)
Other	14 (33.3%)

[a]One subject was diagnosed with breast cancer stage IIIB.

Discussion

Adult onset weight gain is a risk factor for postmenopausal breast cancer. In addition, a significant percentage of women treated for breast cancer report undesirable weight gain during and after treatment.[7,34] Most available evidence suggests that breast cancer recurrence risk is associated with higher body weight.[1] Excess body weight and body fat are established risk factors for CVD and metabolic disease in postmenopausal women.[35] Because of advances in breast cancer diagnosis and treatment, most survivors of breast cancer are more likely to die of CVD than of breast cancer.[21]

Table 2. Energy Intake and Expenditure in Overweight/Obese Breast Cancer Survivors ($N = 42$)

	Mean	*SD*	*Median*	*Range*
Dietary intake				
Total energy (kcal)	1951.1	883.7	1,736.9	427.7–5,635.5
Carbohydrate (g%)	266.0 (53.1%)	157.6	237.3	48.7–1,064.5
Protein (g%)	84.3 (17.5%)	34.1	84.9	19.8–189.7
Fat (g%)	63.3 (30.1%)	27.0	58.5	17.1–142.4
Saturated fat (g)	21.2	9.4	18.7	7.7–49.9
Monounsaturated fat (g)	23.8	10.7	21.8	5.9–56.0
Polyunsaturated fat (g)	13.1	5.9	11.5	2.3–27.9
Fiber (g)	22.8	12.4	21.2	2.7–77.2
Glycemic load (g)	122.0	71.4	112.0	20.5–473.9
Indicators of energy expenditure				
Resting energy expenditure (kcal/day)	1,303.6	183.9	1,260.0	1,010–1,900
Energy expenditure (kJ)[a]	9,300.4	2,078.9	8,895.4	6,131.7–15,635.1

[a]Includes occupational, leisure, recreational, household, sleep, and other energy expenditure; hours for all activities (including work and sleep) have been proportionally adjusted to equal 24 hours/day.

MetS, a clinically relevant risk factor for CVD and a strong risk factor for diabetes mellitus, was common in our overweight, postmenopausal breast cancer survivors (54.8%) despite a significant number of women receiving lipid-lowering or blood pressure-lowering medications. The women remained at risk for MetS based on having abnormal values of other component traits (i.e., waist circumference, glucose) that are included in the diagnostic criteria for MetS. Of interest, the prevalence in our population was higher than the 34% prevalence found in healthy U.S. women of similar age and BMI (25–30 kg/m^2).[36] This difference may be the result of an unequal matching to the referent population or may be related to our assessment of all potential indicators of MetS, whereas population-based studies may be based on available and not comprehensive assessment of all risk factors.

MetS may also be associated with an increased risk of recurrent breast cancer,[12] a finding that may be explained by the strong correlation between MetS and central adiposity, which is thought to act as a significant source of endogenous estrogen exposure in postmenopausal women.[37] Rock et al.[38] recently reported that serum estrogen levels are positively associated with breast cancer recurrence. MetS may also increase the risk for invasive breast cancer independent of hormonal influences in that MetS has also been shown to upregulate inflammatory, adipose-derived cytokines[14] and select proteases inhibitors, such as serpin.[39]

Our finding that CRP levels are significantly elevated, above referent levels of < 1.0 mg/L for lowered risk of CVD, among overweight breast cancer survivors is important given the association between elevation in CRP levels and risk for CVD among women.[40] Published analyses of associations between CRP and cancer risk are inconsistent and limited.[10,12] A study of 42 breast cancer survivors also found mean the CRP level approximately 60% higher than that of age-matched controls.[41] The elevated levels of CRP in our study may reflect the fact that our population was older and overweight and had an elevated mean waist circumference, all factors shown to be positively associated with elevated CRP.[42] However, referent CRP levels from similarly aged, healthy yet

Table 3. Anthropometric, Body Composition, and Weight History Assessments among Overweight/Obese Breast Cancer Survivors ($N = 42$)

	Mean (SD)	*Median*	*Range*
Anthropometry			
Height (m)	1.6 (0.1)	1.6	1.5–1.8
Weight (kg)	83.8 (12.4)	83.2	64.8–110.0
Body mass index (BMI) (kg/m^2)[a]	31.4 (4.2)	30.5	25.7–39.6
Total body fat (%)[b]	46.9 (5.4)	47.3	35.4–58.7
Lean soft tissue (kg)[b]	40.7 (4.2)	40.6	32.2–52.1
Measures of central adiposity			
Trunk fat (kg)[b]	20.4 (4.9)	20.0	13.4–35.4
Waist circumference (cm)	99.1 (10.1)	98.3	84.0–126.0
Hip circumference (cm)	113.7 (9.7)	112.5	97.0–133.0
Waist/hip ratio	0.9 (0.1)	0.9	0.7–1.1
Weight history (kg)			
Last year	82.5 (13.5)	79.5	53.2–111.4
5 years ago	73.2 (11.6)	70.5	54.6–108.2
High school (16–18)	56.9 (9.0)	55.2	43.2–86.4

[a]Enrollment restricted to BMI $\geq 25 < 40$ kg/m^2.
[b]Measured by dual energy X-ray absorptiometry.

Table 4. Clinical Measurements and Metabolic Syndrome Diagnostic Criteria among Overweight/Obese Breast Cancer Survivors ($N = 42$)

	n (%)	Mean (SD)	Median	Range	Healthy normal
Metabolic biomarkers					
Fasting glucose (mg/dL)		98.7 (12.9)	98	78–149	≤100 mg/dL
OGTT[a] at 2 hours ($n = 23$)		119.0 (32.4)	113	62–192	<140 mg/dL at 2 hours
Insulin (uU/mL)		16.1 (13.2)	13	4–82	5–20 uU/mL
Glycosylated hemoglobin (HbA1c) (%)		6.0 (0.5)	5.8	5.1–7.4	≤5%
Thyroid-stimulating hormone (mIU/L)		2.1 (1.4)	1.7	0.4–7.4	0.4–4.0 mIU/L
Lipid biomarkers					
Triglycerides (TG) (mg/dL)		129.4 (55.7)	120	52–275	<150 mg/dL
Total cholesterol (mg/dL)		199.9 (33.7)	199	104–285	<200 mg/dL
HDL cholesterol (mg/dL)		57.7 (17.5)	56	26–109	≤50 mg/dL
LDL cholesterol (mg/dL)		116.4 (28.6)	109	57–190	<130 mg/dL
Total cholesterol/HDL cholesterol ratio		4.7 (6.4)	3.8	2–45	5:1
Inflammatory biomarker					
C-reactive protein (hsCRP, mg/L)[b]		5.1 (5.3)	3.8	0.6–33.6	<1 mg/L
Hyptertensive indicators					
Systolic blood pressure (mmHg)		129.9 (18.1)	129	101–190	<130 mmHg
Diastolic blood pressure (mmHg)		79.1 (11.5)	78	47–104	<85 mmHg
Classification of metabolic syndrome					
International Diabetes Foundation (IDF) diagnostic[c]	23 (54.8%)	2.5 (1.2)	3	0–5	<3

[a]OGTT, oral glucose tolerance test; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[b]High sensitivity C-reactive protein (hsCRP) healthy normal range indicates low risk of cardiovascular disease, 1–3 mg/L moderate risk, >3 mg/L high risk.
[c]For IDF diagnostic, patient must have 3 or more of the following: TG ≥150 mg/dL, waist circumference >88 cm, fasting glucose ≥100 mg/dL (revised based on American Diabetes Association recommendation for glucose cut point) or diabetes medication, systolic or diastolic blood pressure ≥130 or 85 mmHg, respectively, HDL ≤50 mg/dL.

overweight women[33] did not show similarities in mean elevations as was shown in our population. The reasons for the particularly high mean CRP levels in this population, which are consistent with levels reported among breast cancer patients enrolled in the Fairey et al. study,[43] are unknown but may exist secondary to concomitant hormonal therapies,[44] prior cancer therapies,[41,45] and possibly an underlying higher baseline inflammatory state in women at risk for breast cancer.[46] Over 70% of women in our study population were prescribed aromatase inhibitors, and just over 23% were prescribed tamoxifen. It is possible that these estrogen-modifying medications could contribute to abnormal CRP levels; available data are sparse. One study by Jones et al.[41] of 47 breast cancer patients and 11 age-matched controls showed CRP levels to be approximately 70% higher in women who received chemoendocrine therapy, a clinical risk that was accompanied with significantly reduced cardiac output. However, a recent epidemiological analysis from the the Health, Eating, Activity and Lifestyle (HEAL) study suggested that tamoxifen use was associated with reduced CRP levels in a population of 741 breast cancer survivors,[47] and raloxifene, another estrogen receptor modulating agent, has also been associated with reduced CRP levels in healthy adult females.

Analyses of associations between CRP levels and the risk of breast cancer recurrence are inconsistent and limited.[10,11,13] The same analysis from the HEAL study showed significant positive correlations between CRP and BMI and an inverse association with physical activity.[42] A pilot study by Fairey et al.,[43] testing the efficacy of an exercise intervention to modulate CRP levels showed a favorable but nonsignificant reduction in CRP levels among 53 breast cancer survivors ($p = 0.066$). Of note, women enrolled in the Fairey study had measured baseline CRP levels averaging 5.19 and 4.29 for the exercise and control groups, respectively, values elevated similar to those in our study population. Thus, lifestyle counseling may prove to be beneficial in favorably modifying CRP levels in this population.

These findings are limited by the low number of study subjects, the lack of diversity in terms of race/ethnicity, body weight, and age, and the lack of a control group for comparison. However, they support the hypothesis that MetS is highly prevalent in overweight breast cancer survivors. The high rate of MetS found in our patients was despite the frequent use of statins and antihypertensive medications, suggesting that clinicians should evaluate the entire composite criteria for diagnosing MetS routinely when assessing a breast cancer survivor's CVD risk. CVD is the leading cause of death in women with early stage postmenopausal breast cancer. By better understanding and modulating CVD risk factors associated with overweight breast cancer survivors, primary care providers can positively impact their long-term morbidity and mortality. Lifestyle interventions using diet and physical activity interventions and targeting weight control along with improvements in metabolic indicators should be routinely prescribed for overweight breast cancer survivors, given the relatively high prevalence of MetS shown here and the concern that early-age-of-onset CVD may be contributing to premature death in this patient population.

Clinical implications

The population of breast cancer survivors is increasing significantly, particularly among women with estrogen receptor-positive tumors that are responsive to antiestrogenic medications. Although their cancer prognosis has generally improved, there is growing interest in and perhaps concern about the comorbidities this clinical population may face related to the cancer therapy received and suboptimal lifestyle choices that have contributed to excess adiposity over adulthood. Addressing the need to modify risk factors for CVD, such as diet, physical activity, and body weight/central adiposity, with this patient population early and routinely should result in a reduction in their risk for noncancer-related morbidity and mortality.

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Disclosure Statement

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