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Effects of a Weight Loss Intervention on Body Mass, Fitness, and Inflammatory Biomarkers in Overweight or Obese Breast Cancer Survivors

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Abstract
Background Obesity is characterized by chronic mild inflammation and may influence the risk and progression of cancer.
Purpose The current study is an exploratory analysis of the effect of a weight loss intervention that emphasized increased physical activity on inflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6], interleukin-8 [IL-8], and vascular endothelial growth factor [VEGF]) at the end of the 16-week intervention period in overweight breast cancer survivors.
Methods Study participants averaged 56 years of age (N=68). Intervention participants (n=44 vs. 24 controls) participated in a cognitive behavioral therapy-based weight management program as part of an exploratory randomized trial. The intervention incorporated strategies to promote increased physical activity and diet modification. Baseline and 16-week data included height, weight, body composition, physical activity level, and biomarkers IL-6, IL-8, TNF-α, and VEGF.
Results Weight loss was significantly greater in the intervention group than controls (−5.7 [3.5] vs. 0.2 [4.1] kg, P<0.001). Paired t tests noted favorable changes in physical activity level (P<0.001 intervention, P=0.70 control), marginally lower IL-6 levels (P=0.06 intervention, P=0.25 control) at 16 weeks for participants in the intervention group, and lower TNF-α levels for participants in the intervention (P<0.05) and control groups (P<0.001). Increased physical activity was associated with favorable changes in IL-6 for participants in the intervention group (R^2=0.18; P<0.03).
Conclusion Favorable changes in cytokine levels were observed in association with weight loss in this exploratory study with overweight breast cancer survivors.

Keywords Weight loss · Physical activity · Exercise · Inflammatory factors · Obesity · Breast cancer survivors

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Introduction

Breast cancer is the most common invasive cancer among women in developed countries. It accounts for 26% of incident cancers and 15% of cancer deaths among women in the US, with an estimated 180,000 women diagnosed with breast cancer in 2008 [1]. Most breast cancers are now diagnosed at a localized stage, which is associated with a 5-year survival rate of 96% [1]. In addition, improvements in initial treatments have resulted in an ever-increasing number of breast cancer survivors [1, 2]. Recurrence, risks for second primary cancers, and comorbidities, such as diabetes, cardiovascular disease, and osteoporosis, are issues that need to be considered in long-term management of these women [3, 4].

Overweight or obesity is a negative prognostic factor in both pre- and postmenopausal breast cancer [5, 6], and it is increasingly being recognized as a medical condition that is characterized by chronic mild inflammation [7]. Several

mechanisms have been proposed to explain the adverse effect of overweight on prognosis after the diagnosis of breast cancer, including the unfavorable effects of obesity on circulating levels of inflammatory cytokines [8]. Inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF), have been consistently associated with breast pathology, and specifically, the development of breast cancer [9]. This is possibly a result of their regulatory impact on proliferation of breast cancer cells through estrogen production [10]. Even though the exact processes with which these cytokines may influence breast carcinoma is still under debate [11], higher levels of IL-6 and IL-8 are both associated with advanced disease and/or metastases in breast cancer patients [12]. In addition to influencing the risk and progression of cancer [13, 14], research efforts have identified chronic mild inflammation as an independent predictor of several other chronic diseases and mortality [15].

One probable explanation for the relationship between obesity and inflammation is the finding that adipose tissue functions as a major secretory organ for inflammatory markers, including TNF-α, IL-6, IL-8, and VEGF [14, 16, 17]. Furthermore, increased production and release of TNF-α, IL-6, and IL-8 by adipose tissue are associated with degree of obesity [8, 16]. Conversely, weight loss has been associated with a reduction in these inflammatory factors [18]. Most studies evaluating the influence of weight loss on cytokine levels relied primarily on reduced energy intake as a behavioral strategy [8, 19]. In a randomized clinical trial of weight loss and chronic inflammation in obese adults, Nicklas et al. [15] found that diet-induced weight loss of 5.7% on average resulted in significant reductions in concentrations of IL-6 and TNF-α. In a study with 120 premenopausal obese women (body mass index; BMI≥30 kg/m^2), a reduction in BMI in the intervention group was associated with lower serum levels of IL-6 and C-reactive protein (CRP) [20]. In a recent review, changes in cytokine levels were noted in all 19 studies designed to evaluate the effects of weight loss and exercise on markers of inflammation [19]. The duration of the interventions ranged from 4-6 weeks to 2 years, with reported weight loss ranging from 3.2% to 30% of body weight.

Physical activity has also been shown to affect local and systemic cytokine production. In several studies, exercise interventions of moderate intensity led to significant reductions in circulating levels of IL-6, TNF-α, and IL-8 in healthy individuals and in patients with cardiovascular disease [21–24]. In other studies, the biological response to exercise was found to be dependent on the intensity and duration of the activity [25].

Although several studies have evaluated the relationship between weight loss, exercise, and circulating cytokine levels in healthy obese individuals [15, 26] or in individuals with various health conditions, these relationships have not been previously examined in overweight breast cancer survivors. The purpose of this study was to specifically examine the relationships between weight loss and physical activity and selected inflammatory markers in breast cancer survivors. Samples were obtained from women who participated in a small randomized trial, the Healthy Weight Management (HWM) Study for Breast Cancer Survivors (2002-2004), which successfully promoted weight loss in overweight or obese subjects assigned to the intervention arm. The current study is an exploratory analysis of the effect of weight loss and increased physical activity on inflammatory cytokines TNF-α, IL-6, IL-8 and VEGF at the end of the 16-week intensive intervention period.

Methods

As a feasibility study, the HWM Study was designed as a randomized clinical trial to develop and test a multifaceted approach to promoting healthy weight management in the target population of overweight or obese breast cancer survivors. The intervention incorporated new elements of cognitive behavioral therapy for obesity, such as stronger emphasis on weight maintenance skills. Increased physical activity to promote maintenance of (or increase in) lean body mass, diet modification to facilitate an energy imbalance, and strategies to improve body image and self-acceptance were also emphasized as part of the program.

Participants

The participants in the HWM Study were 85 breast cancer survivors living in San Diego, CA, USA. Primary recruitment procedures included community outreach and networking with clinical contacts to receive referrals. Other strategies included advertising in a major local newspaper and setting up booths at community events. Finally, a list of potentially eligible participants from the University of California, San Diego Cancer Registry was requested. A letter was sent to those on the list inviting them to contact the study coordinator if they were interested in participating in the study.

The inclusion criteria for the study were: 18 years and older; diagnosed with stage I-IIIA breast cancer within the previous 14 years; completed initial treatments (i.e., surgery, adjuvant chemotherapy, radiation therapy); initial BMI≥25.0 kg/m^2 (overweight or obese) and a minimum of 15 kg over ideal weight as defined by the Metropolitan Life Insurance Company tables [27]; willingness and ability to attend group meetings for 16 weeks and to maintain contact

with the investigators for 1 year; and ability to provide dietary and exercise data by telephone at prescribed intervals. An exclusion criterion was the inability to participate in physical activity because of severe disability (e.g., severe arthritic conditions).

At screening and recruitment, the ability to participate in mild and moderate physical activity was assessed with the Physical Activity Readiness Questionnaire and Health History Questionnaire, a standard procedure for screening participants for community-based physical activity programs of this nature [28]. Following recruitment and written consent, participants were stratified by BMI [(25.0-29.9 (n=38) versus >30.0 (n=47)kg/m^2)] and age [<=50 (n=26), 51-65 (n=47), >65 (n =12)], and randomly assigned to either the group-based intervention program (n=56) or a control group (n=29), with a 2:1 intervention-to-control ratio to provide sufficient statistical power for the main study hypothesis (differential weight loss between groups), while minimizing subject numbers in this feasibility study. A test of two-sample comparison of the 16-week weight change scores was selected with the alpha (type one error) level set at 0.025 assuming a Bonferroni correction for multiple hypothesis tests. The power (or one minus the type two error) was 80%. The standard deviation for weight change, assumed equal in both groups at 16 weeks, was set at 5.2 kg based on data from Andersen et al. [29]. This sample size analysis indicated that a final number of 63 participants (42 intervention and 21 control), after accounting for dropouts, would provide an adequately powered comparison to detect a clinically significant effect size. Figure 1 includes the CONSORT flow chart for the HWM study.

Weight Loss Intervention

The intervention sessions were led by trained investigators and research staff. The program curriculum consisted of group sessions provided according to the following schedule: weekly for 4 months, and follow-up monthly sessions through 12 months. The primary goal of the intervention was to promote regular physical activity and reduced energy intake in order to facilitate weight loss (Fig. 2). The group meetings consisted of discussion and educational/didactic sessions that covered the content areas, with the major proportion of time devoted to increasing physical activity. All intervention subjects also received intensive individualized telephone-based counseling from the study coordinator, starting with weekly calls and decreasing in frequency after the first month (every other week for the next 2 months, and once a month thereafter). The time points for data collection from all subjects were baseline, 16 weeks, and 12 months. The group sessions offered to the treatment study arm was closed-group contingents (with an average of 12-15 women). To equalize possible seasonal effects on targeted behaviors and weight change in the two study arms, wait list subjects were followed concurrent with intervention group subjects and received general contact such as mailed communications during the study period. At study end, they were provided all written intervention materials and a concise version of the didactic material along with facilitated discussion in the format of a 2-day seminar.

Measures

Anthropometric measurements (height, weight, and waist and hip circumferences) were collected at baseline and 16 weeks using standard procedures, and body composition was measured with dual energy X-ray absorptiometry (DXA) using a Lunar DPX-NT densitometer (Lunar/GE Corp). Whole body, regional body fat, and percent fat were obtained from total body DXA scans. All scans were conducted by the same certified technician who was blinded on the assignment of the intervention for each participant.

Physical activity data were collected at baseline and 16 weeks using the 7-day physical activity recall instrument developed by Blair et al. [30]. This approach has been shown to be highly reliable (test-retest reliability=0.99) [31], valid, and sensitive to the effects of physical activity promotion programs [30]. This instrument focuses on the participant's daily activities over a 7-day period. A telephone interview is scheduled and the interviewer asks the participant to recall when and what kind of physical activity they had in the past week, and the intensity of their activity. Examples of moderate, hard, and very hard activities are provided to help them accurately identify the intensity.

Physical fitness data were collected with the 3-min stepping test, which was used to detect possible changes in aerobic fitness by measuring heart rate during the first 15 s of recovery from stepping. The stepping test has high reliability (0.92), is sensitive to change [32], and widely used to assess cardiorespiratory fitness [33].

Blood Sampling and Assays Blood samples were collected at baseline and 16 weeks between the hours of 8 AM and 1 PM for a majority of the participants (83% at baseline, 68% at 16 weeks). Following centrifugation and separation, plasma or serum was stored at −80^o C until assays were conducted. Levels of IL-6, TNF-α, IL-8, and VEGF were determined in duplicate by commercial ELISA with internal controls (R&D Systems, Mpls, MN). Intra-assay coefficient of variation (CVs) were <8%, and inter-assay CVs were <7%. Both samples from a given participant were assayed together [34].

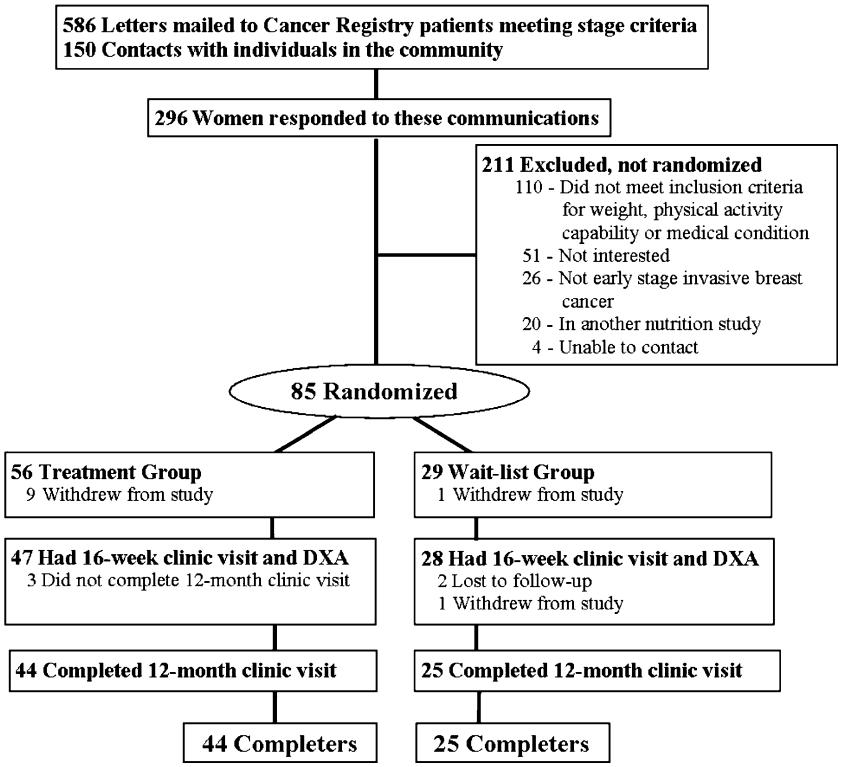

Fig. 1 CONSORT Chart for Healthy Weight Management Study including recruitment information

Components of the intervention The overall content of the intervention included behavioral and cognitive strategies for implementing dietary modification and increasing physical activity [35]. The goal was to achieve a modest weight loss that is sustained, with an emphasis on features that increase this likelihood, such as acceptance of modest weight loss and focusing on skills for weight maintenance. The physical activity component involved encouraging and promoting regular planned aerobic exercise. The long-term goal was to achieve an average of at least 1 h/day of planned exercise at a moderate level of intensity, which is consistent with the current Institute of Medicine recommendations [36]. The main goal of the dietary guidance component was to promote a reduction in energy intake

Session	Topic	Session	Topic	Session	Topic
1	Introduction. Identifying initial goals: Meal planning, daily exercise.	9	Cognitive aspects: Self talk/affirmations. Exercise: Intensity and fatigue.	17	Dietary supplements.
2	Stimulus control and diet. Exercise intensity. Estimating calories.	10	Scientific update: Nutrition and breast cancer, recurrence and progression.	18	Relapse and interruptions.
3	Hands on session: Portion control.	11	Stimulus control for exercise.	19	Overview of behavioral techniques.
4	Body image/Self acceptance. Setting a weight goal. Life style activity (pedometers).	12	Body image and overeating episodes. Challenges of eating out and strategies.	20	Weight maintenance skills.
5	Hands on session: Physical activity.	13	Role of social support.	21	Holidays and interruptions.
6	Time management for exercise. Energy density of diet.	14	Exercise: Fun.	22	Revisiting social support.
7	Benefits/costs of exercise.	15	Exercise: Commitment.	23	Meal satiety.
8	Refine meal plan. Differentiating weight loss and primary goals.	16	Exercise: Mental health and stress management. Cancer and fatigue.	24	Weight maintenance skills.

Fig. 2 Weight loss intervention curriculum topics

Table 1 Characteristics of the study groups at baseline

	Intervention (n=44)	Control (n=24)
Variables	Mean (SD)	Mean (SD)
Age, years	56 (9)	56 (8)
Years of education, years	16 (2)	16 (2)
Body mass index, kg/m^2	30.8 (3.8)	31.3 (5.2)
Weight, kg	83.9 (11.8)	87.2 (14.7)
Waist circumference, cm	101.5 (12.0)	106.7 (13.4)
Total body fat, kg	36.9 (7.5)	40.4 (10.2)
Step test, HR/30 s	60 (8)	57 (7)
Moderate or vigorous physical activity, h/week	3.2 (2.1)	3.7 (3.3)

None of the means are significantly different between groups at baseline

relative to expenditure, with a goal being an energy deficit of 500-1,000 kcal/day by individualized diet modification that emphasized reduced energy density of the overall diet [37], while avoiding excessive dietary restraint. The wait list group participants were provided only general contact (monthly check-up calls, holiday and seasonal cards, and mailed communications) without specific reference to weight management topics through a 12-month period of data collection. Following that period, they were provided all written intervention materials and a concise version of the didactic material, and facilitated discussion was offered in the format of a 2-day seminar.

Data Analysis

Data were analyzed on all participants (n=68) who had data for weight, waist, percent body fat, physical fitness, physical activity, and inflammatory cytokines at baseline and 16 weeks, following the intensive intervention period, to explore the association between weight loss (independent variable) and change in each inflammatory factor (dependent variable). The relationship between physical activity (independent variable) and change in inflammatory biomarkers was also examined. Although 12 month data were collected as part of the parent study, the present findings describe data from the 16-week data collection period when blood samples were analyzed for cytokine assays.

Change variables were computed to evaluate group differences in key study outcomes, such as BMI, weight, body composition, and level of physical activity. Group differences in outcome variables at 16 weeks between the intervention and control groups were assessed with independent t tests. After excluding values of cytokine data that exceeded three standard deviations from the overall mean, within group differences between baseline and 16 weeks were evaluated with paired t tests. Spearman correlations (excluding outliers) examined relationships between cytokines, BMI, percent body fat, and physical activity at baseline and at 16 weeks. Regression analyses explored the association between the increase in physical activity levels (independent variable) and change in each inflammatory factor (dependent variable), controlling for weight loss and change in stepping test heart rate. An alpha value ≤ 0.05 was considered statistically significant. Data were analyzed using SPSS for Windows, Version 11.5 (2002) and SAS statistical software, version 9.2 (2008).

Results

Participant ranged from 33 to 71 years of age. Ninety-four percent of the participants were non-Hispanic white. The majority of the participants were married (77%), and many had completed college or higher levels of education. No significant differences were found between intervention and control groups for demographic characteristics such as age,

Table 2 Mean differences in magnitude of change for key variables between baseline and 16 weeks

[a] One control and two intervention subjects had missing body composition data (one intervention at baseline; one intervention and one control at 16 weeks)

*P<0.05; **P<0.0001

Mean (SD)	Intervention (n=44)	Control (n=24)
Change in body mass index, kg/m2	−2.1 (1.3)**	−0.1 (1.5)
Change in weight, kg	−5.7 (3.5)**	−0.2 (4.1)
Change in waist circumference, cm	−7.1 (6.4)*	−2.5 (7.7)
Change in percent body fat[a]	−4.5 (3.8)**	−0.9 (2.3)
Change in step test, HR/30 s	−6.0 (8)*	−1.0 (6)
Change in physical activity levels, h/week	2.2 (3.3)*	0.3 (3.7)

Table 3 Within group differences for change in cytokine levels between baseline and 16 weeks

	Intervention				Control			
Mean (SD) Variables	*N*	Baseline Mean (SD)	16 Weeks Mean (SD)	*P* value	*N*	Baseline Mean (SD)	16 Weeks Mean (SD)	*P* value
TNFα (pg/mL)	42	5.9 (2.0)	5.4 (1.9)	0.03	24	5.4 (1.3)	4.6 (1.0)	0.0001
IL-6 (pg/mL)	43	1.7 (0.9)	1.4 (0.9)	0.06	24	1.7 (1.3)	1.4 (0.8)	0.33
IL-8 (pg/mL)	43	4.8 (1.7)	5.1 (2.0)	0.29	23	4.5 (1.5)	4.4 (1.9)	0.75
VEGF (pg/mL)	42	29.3 (21.8)	33.5 (27.0)	0.20	23	34.9 (22.5)	31.3 (16.6)	0.38

IL-6 interleukin-6, *IL-8* interleukin-8, *TNF-α* tumor necrosis factor-α, and *VEGF* vascular endothelial growth factor

Three sigma outliers (one each for IL-6, IL-8, and VEGF and one for both Il-6 and VEGF in the intervention group; one each for IL-8 and VEGF in the control group) were excluded

level of education, and race/ethnicity. Similarly, no differences at baseline were observed for outcome measures such as BMI, weight, and physical fitness or activity levels (Table 1).

According to independent *t* tests, the magnitude of reduction in BMI ($P<0.0001$), weight (−6.8% in intervention and −0.3% in control, $P<0.0001$), waist circumference ($P<0.05$), and percent body fat ($P<0.0001$) between baseline and 16 weeks was significantly greater for participants in the intervention group (Table 2). Additionally, performance on the stepping test indicated better fitness ($P<0.05$), and hours of moderate or vigorous physical activity, between baseline and 16 weeks improved significantly more for participants in the intervention group than for controls ($P<0.05$; Table 2).

According to paired *t* tests evaluating within-group differences in inflammatory factors for the intervention group between baseline and 16 weeks, levels of TNF-α significantly reduced ($P<0.05$). A reduction was also noted for IL-6 level ($P=0.06$; Table 3). TNF-α was also found to be decreased at 16 weeks for the control group ($P<0.05$; Table 3). No differences were noted for IL-8 and VEGF.

Correlation analysis showed that several inflammatory factors were associated with key outcome measures for the participants in the intervention group. Both IL-6 and VEGF were positively correlated with BMI at 16 weeks ($r=0.37$, $P<0.05$ for IL-6, and $r=0.44$, $P<0.01$ for VEGF). IL-6 levels at 16 weeks were also positively correlated with performance on step test ($r=0.42$, $P<0.01$). Increased total hours of moderate or vigorous exercise at 16 weeks was correlated with favorable reductions in IL-6 ($r=-0.35$, $P<0.05$) and VEGF ($r=-0.46$, $P<0.01$) between baseline and 16 weeks.

In a regression analysis using participants in the intervention group, controlling for change in weight and change in heart rate/min after the stepping test, increased level of physical activity was associated with favorable changes in IL-6 levels ($R^2=0.18$, $P<0.05$; Table 4). Other cytokines did not show significant associations with change in physical activity.

Discussion

Several possible mechanisms by which weight loss and physical activity may play a role in reducing breast cancer risk have been proposed [38]. This small randomized clinical trial provides an opportunity to evaluate the short-term effects of weight loss and increased physical activity on circulating cytokines IL-6, IL-8, TNF-α and VEGF in overweight or obese breast cancer survivors.

Participants in this study lost nearly 7% of body weight at the end of the intensive intervention period at 16 weeks. They also reported increased physical activity and demonstrated improved cardiorespiratory fitness at this time point. These findings have promising public health implications because the vast majority of women who have been diagnosed with breast cancer are overweight or obese and exercise at very low levels of intensity and duration [39–41]. Also, concern with overweight and weight gain is a

Table 4 Regression model of factors associated with IL-6 levels at 16 weeks in the intervention group ($n=38$)

Variable	β-coefficient	Significance (*P* value)	R^2
Increase in moderate or vigorous physical activity, hours/week	−0.125	0.02	
Change in weight, kg	0.01	0.2	
Change in heart rate/min after step test	−0.01	0.7	
			0.18

Excluding one 3-sigma outlier

common complaint among breast cancer survivors [42]. In a comprehensive review of observational studies on breast cancer recurrence or survival, Rock and Demark-Wahnefried [6] reported that increased BMI and/or excessive adiposity is a significant risk factor for recurrent disease and/or decreased survival in a majority of the studies. The findings from this exploratory study suggest that increased levels of physical activity and weight loss achieved by participants in this weight loss intervention may positively influence the rates of survival in these women by reducing overall inflammation [19].

The current study also explored changes in levels of circulating cytokines in these overweight and obese breast cancer survivors because inflammatory cytokines are thought to increase with the degree of adiposity [16], and weight loss has been associated with a reduction in the levels of inflammatory factors in the general population. An association with breast pathology and inflammatory cytokines has been noted in previous research studies [9]. In addition to losing a notable amount of weight, participants in the intervention group reported an increase in level of moderate or vigorous physical activity and improved fitness. During that time period, levels of two inflammatory factors declined; IL-6 for the intervention group and TNF-α for both groups. The observation of a decrease in TNF-α for the control group suggests that the relationship between obesity and TNF-α production by adipose tissue may not be clearly established. Recently, Bastard et al. [18] concluded that the precise role of TNF-α in human obesity needs further investigation because adipose tissue does not seem to be directly implicated in the increased circulating TNF-α levels observed in obese humans. Evidence from other studies suggest lower levels of TNF-α in breast cancer patients and a possible anti-tumor effect on breast cancer cells [12], in addition to its effects on promoting cellular transformation and metastasis [38]. The precise role of TNF-α in relation to obesity and physical activity needs to be investigated further in order to better understand the decline observed in this study.

We also observed positive associations for BMI, percent body fat, and IL-6 after the intensive intervention period of 16 weeks. Similar significant positive associations with CRP, BMI, and waist circumference were identified in a recent study with breast cancer survivors [43, 44]. Further, the reduction in IL-6 level was correlated with increased total hours of moderate or vigorous physical activity in both univariate and multivariate analysis. These findings are noteworthy, because even though previous studies have shown that increased exercise may reduce the levels of circulating inflammatory factors [21–23], similar findings have not been previously reported in breast cancer survivors. In a review of the biological mechanisms that may explain the affect of physical activity on breast cancer risk, Neilson et al. [38] concluded that even though weight loss can decrease levels of IL-6, physical activity may alter IL-6 levels through an independent mechanism that is not yet well-understood.

These findings provide some insight into the relationship between weight loss, increased physical activity, and inflammatory cytokines, supporting the suggestion that further research should be pursued in this arena. Even though higher cytokine levels have been associated with increased disease risk across studies, identifying the magnitude of change that could be considered beneficial for health outcomes remains a challenge, possibly as a result of multiple factors effecting this relationship [45, 46]. Future research aiming to determine effective levels of change in cytokines in response to weight loss or increased physical activity would be valuable. Due to the small sample size, the findings from the current study should be considered exploratory. Moreover, because the participants in this study were mostly non-Hispanic whites, the results might not be generalizable to breast cancer survivors representing other racial/ethnic groups.

Understanding the complex associations between obesity, physical activity, and cytokine levels as they relate to breast cancer risk has clinical implications because of the potential roles they may play as part of immunotherapic interventions [12, 47]. Findings from this study contribute to exploring the mechanisms by which excessive adiposity increases risk for recurrence and reduces likelihood of survival following the diagnosis and treatment of early stage breast cancer. The findings also contribute to the knowledge base of the complex interactions between inflammatory factors and morbidity and mortality relating to cancer.

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