Research Article

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Exercise-Induced Dose–Response Alterations in Adiponectin and Leptin Levels Are Dependent on Body Fat Changes in Women at Risk for Breast Cancer

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Abstract

Background: Dysregulation of adipokines, such as adiponectin and leptin, is associated with a variety of chronic diseases, including cancer. Physical activity protects against breast cancer and one of the mechanisms which may underlie this association is exercise-induced changes in adipokine levels. The WISER Sister Trial was a three-armed randomized controlled trial in premenopausal women ($n = 137$) with an elevated risk for breast cancer.

Methods: A 5-menstrual-cycle-long dosed aerobic exercise intervention compared low-dose exercise (150 min/wk; $n = 44$) or high-dose exercise (300 min/wk; $n = 48$) with a control group asked to maintain usual activity levels ($n = 45$). Exercise intensity progressed to and was maintained at 70% to 80% of age predicted heart rate max. Body composition and adipokine levels were measured at baseline and follow-up.

Results: We observed significant linear trends for increased fitness capacity (Δ%: −2.0% control, 10.1% low dose, 13.1% high dose), decreased fat tissue-to-total tissue mass (Δ%: 0.7% control, −2.9% low dose, −3.7% high dose), increased body fat adjusted adiponectin (Δ%: −0.6% control, 0.6% low dose, 0.9% high dose), and decreased body fat adjusted leptin (Δ%: 0.7% control, −8.2% low dose, −10.2% high dose).

Conclusions: In this randomized clinical trial of premenopausal women at risk for breast cancer, we demonstrate a dose–response effect of exercise on adiponectin and leptin and that dose response is dependent on changes in body fat.

Impact: Improved adipokine levels, achieved by aerobic exercise training–induced decreases in body fat, may decrease breast cancer risk for high-risk premenopausal women. *Cancer Epidemiol Biomarkers Prev; 25(8); 1195–200. ©2016 AACR.*

Introduction

Physical activity protects against both pre- and postmenopausal breast cancer. In a meta-analysis which quantified data from 31 studies, breast cancer risk was found to decrease by 2% for every 25 MET-h/wk increment in nonoccupational activity, 3% for every 10 MET-h/wk increment in recreational activity, and 5% for every 2 h/wk increment in moderate plus vigorous recreational activity (1). Specific to premenopausal physical activity, exercise (39+ MET-h/wk on average) before menopause is associated with a 23% lower risk of premenopausal breast cancer (2). Mechanisms proposed to explain the ability of higher levels of physical activity to prevent breast cancer include the beneficial effects of activity on hormonal exposures, metabolic hormones, immune function, inflammation, and adipokines (3). The adipose tissue microenvironment is an important element in breast cancer development; therefore, we investigated the effect of physical activity on circulating adipokine levels (adiponectin and leptin).

Both leptin and adiponectin are adipose-derived proteins which have pathologic signaling cascades in relationship to breast cancer (4). Leptin stimulates proliferation, migration, and invasion of MDA-MB-231 and MCF-7 breast cancer cell lines (5, 6). Furthermore, leptin and leptin receptors are overexpressed in 70% to 80% of breast cancer tumors (7). While elevated leptin appears to be detrimental, blunted serum adiponectin levels are associated with aggressive tumor phenotypes (8). Mice with reduced adiponectin expression show earlier tumor onset (9). Indeed, adiponectin has been shown to block proliferation of several breast cancer cells lines (10).

Exercise is a systemic therapy that can modulate biomarkers potentially involved in breast cancer pathways. Preclinical models demonstrate improved leptin sensitivity and enhanced adiponectin expression (11, 12). Clinical trials utilizing exercise interventions report decreased leptin levels but mixed results with regard to increasing adiponectin levels (13–17). In addition, it is difficult to determine the independent effects of exercise on adipokine levels as alterations in body composition are often not controlled. Furthermore, there have been no dose–response randomized clinical trials (RCT) to date.

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Changes in adiponectin and leptin levels may be dependent on the population being investigated, the dose of exercise, and possible concomitant changes in body composition. Therefore, because of the link between adipokines and breast cancer, we investigated the effect of exercise on adiponectin and leptin levels and their relationship with changes in body composition in premenopausal women at elevated risk for breast cancer. We conducted a randomized controlled trial in a high-risk population utilizing a dosed exercise intervention (150 min/wk and 300 min/wk).

Materials and Methods

Complete study design and methods are available and have been previously published (18). In the Women In Steady Exercise Research (WISER) Sister study, conducted at the University of Pennsylvania (Philadelphia, PA), premenopausal women with an elevated risk for breast cancer were recruited nationally for a 5-menstrual-cycle-long exercise intervention. Recruitment for the study was conducted from December 2008 to March 2012 and occurred through the Facing Our Risk of Cancer Empowered (FORCE) organization, the Cancer Genetics Network, genetic counselors, dissemination of brochures through survivorship conferences, and maintaining a web presence. Through these efforts, 1,025 women contacted the WISER Sister study team with interest in participating and were eligible on the basis of initial screening. Following full screening for eligibility, 217 women were eligible for the WISER Sister study, 162 women consented, 139 women were randomized, and 137 had available blood samples for adipokine analysis (18). Of the 137 women, 23% were local participants (residing within 75 miles of the University of Pennsylvania) and 77% were long-distance participants. Eligibility criteria consisted of: age $\geq$ 18 years; eumennorheic; nonsmokers; body–mass index (BMI) between 18 and 50 kg/m^2; no history of fibroids, endometriosis, or polycystic ovary syndrome; no recent use of hormonal contraception; no contraindications for exercise training; controlled hypertension; weight stable; and sedentary (<75 minutes of aerobic exercise per week). In addition, elevated risk for breast cancer was defined as >18% lifetime risk of breast cancer according to Gail or Claus predication models, or documented deleterious mutation of *BRCA1* or *BRCA2*, or documentation of a family member with a known deleterious mutation which would confer a 25% or greater probability of a deleterious mutation in the participant. This study was approved by the University of Pennsylvania Human Subjects Review Committee, and written informed consent was obtained from all subjects before beginning study activities.

Women were randomized with equal chance into 1 of 3 parallel arms. Randomization was done within the strata formed by BMI (baseline BMI was divided by above vs. below 30 kg/m^2) and menstrual age (years since starting menstruation was dichotomized to above and below 10 years). Treatment groups consisted of a control group and 2 intervention groups. The control group was asked to maintain their usual level of physical activity and to not engage in any new exercise program during study participation. The low-dose exercise group completed 150 min/wk, and the high-dose group completed 300 min/wk. Following orientation on proper use of the treadmill, heart rate monitors, and instruction on warm-up, cool-down, stretches, and exercise log completion, a treadmill was shipped to the participant's home. Participants engaged in the 5-menstrual-cycle-long intervention at home and were monitored for adherence through several methods. Exercise logs (date, time, location of workout, and type of equipment used, average heart rate from their heart rate monitor, duration of workout and stretching) were overread by the study staff. Objective heart rate monitors were worn during exercise. Data were downloaded to the University of Pennsylvania. Study staff reviewed exercise logs and heart rate data weekly and would contact women after missed sessions to encourage adherence. Exercise intensity was set at 65% to 70% of age predicted maximum heart rate (220-age) for the first four weeks and 70% to 80% for the remainder of the study. The high-dose exercise group started at 150 min/wk and increased 20 to 25 minutes every 2 weeks until reaching 300 minutes. Further detailed descriptions of the intervention and study parameters have been presented by Schmitz and colleagues (18).

Physical activity was assessed by the Modifiable Activity Questionnaire, and fitness level was determined using the Bruce protocol (19–21). Body composition was evaluated by dual-energy x-ray absorptiometry (DXA; Hologic) and all scans were analyzed by APEX 3.3. Dietary intake was measured through 3-day dietary records, and participants were asked to maintain their normal caloric intake throughout the study. These metrics were completed at baseline and follow-up as previously described (18).

All assessments were completed at the University of Pennsylvania on the same day. Baseline and follow-up visits were scheduled between days 6 and 10 of the menstrual cycle. Plasma from blood draws was stored at -80°C until analysis of adipokines by the University of Pennsylvania Diabetes Core. Adiponectin and leptin were measured by ELISA (R&D Systems and Diagnostic Systems labs, respectively). Adiponectin intra- and interassay coefficients of variation were 16.9 and 15.4, respectively. Leptin intra- and interassay coefficients of variation were 7.5 and 8.4, respectively.

Paired *t* tests were used to assess change within group. A one-way ANOVA was used to test for differences in percent change of variables between intervention groups. Linear regression using percent change variables was used to evaluate intervention effects on adipokines following adjustment for percent change in body fat. An extension of the Wilcoxon rank-sum test was used to test for linear trends across groups. Statistical analyses were conducted using STATA version 12 (Stata Corp.), and statistical significance was set at an alpha level of $P < 0.05$.

Results

Demographic characteristics of the study participants are depicted in Table 1. The age of the 137 participants ranged from 18 to 49 years of age. The majority of women were overweight, non-Hispanic white, married, and college graduates. Women randomized to the low-dose group were more likely to be married and have children, but this difference between groups did not affect other outcomes.

Sixteen women did not complete the study. We observed the following attrition: 1 woman from the control group, 6 women from the low-dose group, and 9 women from the high-dose group. In total, the intervention groups completed more than 80% of the prescribed minutes (low dose, 85%; high dose, 81%). Participants (76%) in the low-dose group had greater than 80% adherence and 75% of participants in the high-dose group had greater than 80% adherence.

Table 1. Demographic characteristics of randomized women

Variable	Total sample ($n = 137$)	Control ($n = 45$)	Low dose ($n = 44$)	High dose ($n = 48$)	*P*
Age, y	34.3 ± 6.92	34.5 ± 7.54	35.1 ± 6.45	33.5 ± 6.75	0.46
BMI, kg/m^2	26.8 ± 6.21	27.0 ± 6.13	26.7 ± 6.06	26.6 ± 6.53	0.96
Caloric intake, kcal/d	1732.8 ± 737.35	1629.2 ± 526.53	1883.7 ± 775.67	1691.6 ± 854.34	0.24
Children, *n* (%)					
Yes	82 (59.9%)	23 (51.1%)	34 (77.3%)	25 (52.1%)	0.01
Marital status, *n* (%)					
Married/partnered	83 (60.6%)	22 (48.9%)	34 (77.3%)	27 (56.2%)	0.01
Race, *n* (%)					
White	116 (84.7%)	38 (84.4%)	39 (88.6%)	39 (81.2%)	0.62
Non-white	21 (15.3%)	7 (15.6%)	5 (11.4%)	9 (18.8%)	
Ethnicity, *n* (%)					
Hispanic	10 (7.3%)	3 (6.7%)	3 (6.8%)	4 (8.3%)	0.94
Education, *n* (%)					
High school or less	4 (2.9%)	3 (6.6%)	1 (2.3%)	0 (0%)	0.43
Some college	40 (29.2%)	12 (26.7%)	13 (29.5%)	15 (31.2%)	
College or more	93 (67.9%)	30 (66.7%)	30 (68.2%)	33 (68.8%)	

NOTE: 137 women with elevated risk for breast cancer (defined as >18% lifetime risk of breast cancer according to Gail or Claus predication models, documented deleterious mutation of *BRCA1* or *BRCA2*, or documentation of a family member with a known deleterious mutation which would confer a 25% or greater probability of a deleterious mutation in the participant) were randomized to control, low-dose exercise (150 min/wk), or high-dose exercise (300 min/wk) groups. Means ± SD.

Following the 5-menstrual-cycle-long intervention, we observed a significant dose–response effect on fitness capacity ($P < 0.001$) as both low- and high-dose participants significantly increased their fitness capacity compared with baseline levels and compared with the control group (Table 2). There were no differences in caloric intake. Energy expenditure decreased in the control group compared with baseline levels, and there was a significant between-group difference in the percent change in physical activity which was significant for a dose–response effect ($P < 0.001$). The control group increased body weight (mass) compared with baseline levels, and there was a significant difference between groups for mass as both low- and high-dose exercise groups lost 0.6% of their body weight ($P = 0.03$; linear trend). The decrease in body weight for the low- and high-dose groups was not due to loss of lean tissue, as we observe increased lean tissue mass compared with baseline for low- and high-dose groups. The low- and high-dose participants did lose fat tissue (kg) and decreased % body fat (fat tissue-to-total tissue mass) compared with baseline levels and compared with the control group. Both of these variables also demonstrated strong linear trends ($P < 0.001$) for a dose–response effect.

Among the 121 women who completed the study, adiponectin levels decreased in the low-dose exercise group compared with their baseline levels and compared with the control group (Table 2 and Fig. 1A – white bars). Leptin levels decreased in the high-dose group compared with their baseline levels. The percent change in leptin levels was not significantly different between any two groups (Table 2 and Fig. 1B – white bars). Given the mechanistic relationship between adipocytes and adipokine levels, we sought to explore the effect of exercise on this relationship. Therefore, we adjusted the observed percent change in adipokines by the percent change in fat tissue-to-total tissue mass for each group. (Fig. 1A and B – black bars). We observed that after controlling for the percent change in body fat, there was a significant increase in adiponectin levels for both exercise groups compared with the control group which decreased adiponectin levels ($P < 0.001$). In addition, after controlling for the percent change in fat tissue-to-total tissue mass, there was a significant decrease in leptin levels for both exercise groups compared with the control group which increased leptin levels ($P < 0.001$). Furthermore, there was an exercise-induced dose–response effect, as there was a significant linear trend across all groups for both adipokines ($P = 0.001$ for both adiponectin and leptin).

On additional analysis of body composition effects on the adipokines, we observed that a decrease in fat tissue ($\beta = -0.8$), as well as fat tissue-to-total tissue mass ($\beta = -1.5$), was associated with a significant increase in adiponectin levels only in the control group (fat tissue $P = 0.02$; fat tissue-to-total tissue mass $P = 0.02$). Decreased mass and fat tissue were significantly associated with decreased leptin levels in all groups, but decreased fat tissue-to-total tissue mass (control, $\beta = 1.7$; low dose, $\beta = 3.0$; high dose, $\beta = 3.2$) was significantly associated with decreased leptin levels only in the exercise intervention groups (control, $P = 0.09$; low dose, $P = 0.01$; high dose, $P = 0.001$).

Discussion

This study investigated the effect of a dosed exercise training intervention (150 or 300 min/wk) on body composition and adipokine levels in premenopausal women at high risk for breast cancer. We observed a significant dose response for enhanced fitness capacity, decreased body fat, and beneficial changes in body fat–adjusted adipokine levels. This study is the first dose–response RCT to date which assesses the effect of volume of exercise on adipokine levels and controls for changes in body composition. In addition, we investigated this relationship in a population in which augmentation of adiponectin, and attenuation of leptin, may be critically important for long-term health outcomes, particularly breast cancer.

Adiponectin levels have an inverse relationship with adiposity levels. Growing evidence suggests that adiponectin inhibits the growth of cancer cells and reduces cancer risk (22). We observed a significant difference between control and low-dose exercise groups, with control participants on average increasing adiponectin levels by 7.3%, whereas participants in the low-dose exercise group decreased adiponectin levels by 6.1%. These results are counterintuitive, as lower levels of adiponectin are associated with increased risk for chronic diseases and a decrease was seen in the low-dose exercise group.

Table 2. Energetics, body composition, and adipokines before and following the exercise training intervention

	Control (n = 44)			Low dose (n = 38)			High dose (n = 39)				
	Baseline	Final	% Δ	Baseline	Final	% Δ	Baseline	Final	%Δ	P % Δ	$P_{linear\ trend}$
Exercise test, min	8.0 ± 1.6	7.8 ± 1.8	−2.0% ± 9.2	8.0 ± 1.6	9.0 ± 1.6[a]	10.1 ± 8.3[b]	8.3 ± 1.9	9.8 ± 1.8[a]	13.1 ± 9.6[b]	<0.001	<0.001
Caloric intake, kcal/d	1845.6 ± 559.3	1821.4 ± 450.3	4.1 ± 30.8	1822.3 ± 559.3	1800.0 ± 542.4	4.2 ± 33.6	1857.4 ± 462.9	1826.1 ± 440.5	1.4 ± 24.8	0.89	0.98
Energy expenditure, MET h/wk	8.4 ± 6.6	2.2 ± 2.3[a]	−63.2 ± 39.4	9.0 ± 9.3	9.0 ± 5.3	250.3 ± 650.6[b]	7.6 ± 6.7	9.8 ± 5.9	295.3 ± 721.7[b]	<0.01	<0.001
Whole body total											
Mass, kg	74.6 ± 16.2	75.7 ± 17.4[a]	1.2 ± 4.5	72.7 ± 17.7	72.2 ± 17.7	-0.6 ± 3.5	69.1 ± 15.1	68.8 ± 15.7	−0.6 ± 3.4	0.04	0.03
Lean tissue, kg	45.4 ± 5.8	45.8 ± 6.3	0.8 ± 3.3	44.1 ± 7.0	44.5 ± 6.7[a]	1.0 ± 2.7	43.6 ± 6.2	44.0 ± 6.1[a]	1.1 ± 2.7	0.89	0.26
Fat tissue, kg	29.2 ± 11.2	29.8 ± 11.9	2.0 ± 8.4	28.5 ± 11.4	27.7 ± 11.7[a]	−3.5 ± 7.3[b]	25.5 ± 10.2	24.7 ± 11.0[a]	−4.2 ± 8.0[b]	<0.001	<0.01
Fat tissue/total tissue mass, %	39.1 ± 6.8	39.3 ± 6.9	0.7 ± 4.5	39.2 ± 6.2	38.1 ± 6.7[a]	−2.9 ± 4.8[b]	36.9 ± 6.8	35.7 ± 7.7[a]	−3.7 ± 5.5[b]	<0.001	<0.01
Adipokines											
Adiponectin, μg/mL	11.9 ± 6.6	12.3 ± 6.0	7.3 ± 19.6	12.3 ± 4.7	11.7 ± 5.1[a]	−6.1 ± 18.6[b]	12.2 ± 4.3	11.9 ± 4.4	−1.3 ± 19.8	<0.01	0.09
Leptin, ng/mL	21.9 ± 13.1	20.5 ± 12.5	−2.5 ± 30.9	18.4 ± 11.2	16.9 ± 11.0	−4.1 ± 36.0	15.9 ± 9.5	14.4 ± 9.9[a]	−10.6 ± 29.26	0.49	0.25

NOTE: Data presented as means ± SD.

[a]$P < 0.05$ within group.

[b]$P < 0.05$ between group on post-hoc Bonferroni testing.

Figure 1.

Percent change values for adiponectin (**A**) and leptin (**B**) are presented as mean ± SD. White bars represent the unadjusted percent change calculation and black bars represent predicted percent change when ([a]) adjusted for percent change in fat tissue-to-total tissue mass. The mediation of adipokine levels by body composition demonstrates a dose–response effect across intervention groups, as we observed significant linear trends. *,†, $P < 0.05$.

Previous reports indicate there is variation with regards to the response of adiponectin levels to exercise, and a review by Simpson reports only 38% of RCTs demonstrate an exercise-induced increase in adiponectin levels (13–15, 23–25). Specific to this investigation, Friedenreich and colleagues reported that a year-long aerobic exercise intervention of 225 min/wk (70%–85% of observed maximal heart rate) did not lead to any differences in adiponectin levels for 320 previously sedentary postmenopausal women (26). Furthermore, Abbenhardt and colleagues utilized the same exercise intervention in a 4-armed RCT that included dietary restriction, exercise, dietary restriction + exercise, and control. Overall, they observed no significant effect of exercise on adiponectin levels, yet the exercise group appears to have decreased adiponectin levels by 7.2% (15). Several other studies which have observed increases in adiponectin levels have observed these changes with concomitant reductions in weight through a weight loss intervention arm and not through exercise (13, 15, 23). In our study, we did not observe between group differences for decreased mass. However, we did observe an exercise-induced dose response for decreased body fat (fat tissue-to-total tissue mass). Given the relationship between adiponectin and adiposity, we adjusted for changes in body fat. Exercise-induced reduction in body fat led to increased adjusted adiponectin levels in a dose-dependent manner. However, a

predicted increase of less than 1% in adiponectin levels may have limited clinical utility. Plasma adiponectin levels in normal subjects have been reported at 5 to 20 μg/mL (27), and adiponectin concentrations of 5 to 25 μg/mL show inhibitory effects on TNFα and adhesion molecule expression (28). Obese subjects have plasma adiponectin levels < 6 μg/mL (29). Thus, exercise-induced changes in body fat which impart a less than 1% increase in plasma adiponectin levels for healthy, premenopausal women have an unknown effect for long-term protection against breast cancer in this at risk cohort.

Another adipokine that is linked epidemiologically with breast cancer risk (30), and also mechanistically to carcinogenesis (31), is leptin. This protein is produced by adipocytes, fibroblasts, and also breast cancer cells once malignancy is present. Therefore, leptin can act in an endocrine, paracrine, as well as autocrine manner. There are complex biologic networks involved with leptin signaling in the breast. Thus, therapeutic interventions to lower leptin levels, and keep it low, are necessary for women at risk for breast cancer.

We observed very similar patterns of decreased leptin levels for unadjusted and adjusted percent change in leptin. The dose response to exercise was apparent with body fat adjustment, but we also observed a significant difference between unadjusted baseline and final levels in leptin for the high-dose exercise group. Our findings are in line with others that have investigated the effect of exercise and changes in body composition on leptin levels (32). Following 12-month aerobic exercise interventions, Abbenhardt and colleagues observed a 13% reduction in leptin levels with exercise and Frank and colleagues a 7% reduction (15, 33). It appears that leptin demonstrates a much more reliable association with body fatness and this association may be due to the high degree of association seen between exercise-induced changes in leptin expression levels and changes in adipocyte size (11).

Our study investigated the adipokines, adiponectin and leptin, as they are recognized for their influence on breast cancer risk and tumor biology. Adipocytes primarily secrete these proteins, but different fat depots play contrasting physiologic roles. Adiponectin and leptin are predominantly secreted by subcutaneous adipose tissue (34, 35). Yet, aerobic exercise training reduces visceral adipose tissue to a greater extent than subcutaneous adipose tissue (36, 37). We saw a significant dose-dependent decrease in body fat as measured by DXA. However, we did not investigate differences between subcutaneous and visceral fat. Given our unexpected unadjusted adiponectin results, the small body fat–adjusted dose response and the variability seen in other studies in response to exercise, there are likely other systemic and metabolic factors influencing adiponectin expression and plasma concentrations (38). For instance, Fatouros and colleagues demonstrated a large effect size for increased adiponectin levels with high-intensity resistance training which was not seen with low or moderate intensities (39). This study highlights how different intensities of exercise and different modalities of exercise (resistance vs. aerobic) may affect adipocyte dysfunction given the unique cross-talk between subcutaneous adipose tissue and skeletal muscle.

Our study is the first randomized controlled trial to examine the effect of a dosed 5-menstrual-cycle-long exercise intervention on circulating adiponectin and leptin in a national cohort of women at risk for breast cancer. A key strength of our study is our high adherence level, particularly in the high-dose exercise group. In addition, this dose–response study investigates volume of exercise through increased duration of exercise. We did not alter exercise intensity between groups, thus allowing for easy adoption for public health recommendations. We also recognize that there are limitations to the current study. While altering volume of exercise through duration is advantageous for implementation, it also leaves the question of intensity unanswered. Furthermore, we measured plasma adiponectin and leptin levels. The relative importance of adipokines as endocrine, paracrine, or autocrine factors is unknown. Thus, the extent to which circulating adipokine levels reflect the potential interaction with the preneoplastic epithelium is also unknown (40).

Overall, preclinical and clinical research points toward a role for adiponectin and leptin in carcinogenesis. Adipose tissue dysfunction affects the production of these adipokines. Thus, keeping body fat at healthy levels is of vital importance for premenopausal women at risk for an obesity-linked disease such as breast cancer. In this study, we demonstrate a dose–response effect of exercise on these adipokines and that dose response is dependent on changes in body fat.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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