

The Effects of Resistance Exercise on Biomarkers of Breast Cancer Prognosis: A Pooled Analysis of Three Randomized Trials

Kerri M. Winters-Stone^{1,2}, Lisa J. Wood³, Sydnee Stoyles^{1,2}, and Nathan F. Dieckmann^{1,2}



Abstract

Background: Using a secondary data analysis from randomized controlled trials comparing one year of resistance exercise ($n = 109$) to a placebo control condition ($n = 106$) in postmenopausal, posttreatment breast cancer survivors, we investigated the influence of resistance training and changes in body composition on markers associated with cancer progression.

Methods: Measures included serum levels of insulin, IGF-1, IGFBP1-3, leptin, serum amyloid A (SAA), adiponectin, C-reactive protein (CRP), IL1 β , TNF α , IL6, and IL8, and body composition (total, lean and fat mass in kg) by DXA at baseline, 6, and 12 months. Linear mixed effects models were used to examine the association between group, biomarkers, and body composition and whether or not changes in muscle strength or body composition influenced the effect of exercise on biomarkers.

Results: CRP decreased over time among women participating in resistance training compared with increases in

controls ($P = 0.045$). In stratified analyses and compared with increases in controls, women who gained strength reduced CRP ($P = 0.003$) and maintained levels of IL1 β and IL6. Among exercisers who lost weight (≥ 2 kg), CRP ($P = 0.045$), leptin ($P < 0.01$), and SAA ($P = 0.029$) decreased, whereas IGF-BP1 ($P = 0.036$) increased compared with controls.

Conclusions: Resistance training may lower inflammation and improve insulin pathway profiles, but the magnitude and degree of benefit from exercise may depend upon whether or not women gained strength, a possible marker of compliance with training, and/or lost weight during exercise.

Impact: Future resistance training trials should consider these potential influencing factors as they may determine how well exercise can slow cancer progression and prevent disease recurrence. *Cancer Epidemiol Biomarkers Prev*; 27(2); 146–53. ©2017 AACR.

Introduction

Observational epidemiologic studies have linked physical activity to improved breast cancer prognosis, but biologic mechanisms responsible for this relationship are not fully understood. Meta-analyses of physical activity and survival outcomes in breast cancer survivors estimate that women who reported regular physical activity after diagnosis have a 34% lower risk of breast cancer death, a 41% lower risk of death from any cause, and a 24% lower risk of breast cancer recurrence than inactive women (1). Although these findings are encouraging, the reasons for this protective effect of physical activity in breast cancer survivors cannot be determined from observational studies. In the absence of controlled clinical trials with survival as an endpoint, exercise

studies that provide data on biomarkers of cancer progression can substantiate epidemiologic reports.

Several potential mechanisms have been proposed to explain the link between physical activity and breast cancer survival, including decreases in systemic inflammatory mediators and metabolic hormones (2–4). Low-level systemic inflammation characterized by elevations in TNF α , IL6, leptin, and CRP is associated with an increased risk of breast cancer progression and mortality (5–7), whereas high levels of insulin and alterations in IGF-1 and its binding proteins have been associated with an increased risk of breast cancer recurrence, breast cancer-related death, and overall mortality (8–11). Exercise might serve as a form of immunotherapy by lowering inflammation (12, 13) and improving insulin pathway regulation (14, 15), but evidence for this effect from a small number of controlled trials that included biological markers linked to cancer progression is limited (16–19).

In addition to establishing the link between physical activity and markers of breast cancer progression, it is important to understand whether certain conditions must be met for exercise to be beneficial (20). Given the relationship between obesity and cancer, it is also important to establish whether or not exercise must alter body weight and composition to favorably shift markers of progression. Studies in noncancer populations have reported that reductions in adiposity are significantly correlated with reductions in CRP among exercisers (21, 22) and that exercise-induced reductions in inflammatory cytokines only occur among participants who lose weight (23). The type and dose of

¹Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon.

²School of Nursing, Oregon Health & Science University, Portland, Oregon.

³School of Nursing, Massachusetts General Hospital Institutes of Health Professions, Boston, Massachusetts.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

ClinicalTrials.gov identifiers: NCT00665080, NCT00659906, NCT00591747.

Corresponding Author: Kerri M. Winters-Stone, Oregon Health & Science University, 3455 SW US Veteran's Hosp Rd, SN-ORD, Portland, OR 97239. Phone: 503-494-0813; Fax: 503-418-0903; E-mail: wintersk@ohsu.edu

doi: 10.1158/1055-9965.EPI-17-0766

©2017 American Association for Cancer Research.

exercise may also be important determinants of whether or not biological pathways of cancer progression are altered. For example, resistance exercise often increases IGF-1 to promote muscle anabolism, but may decrease with aerobic exercise training that is more catabolic (14, 15). With regard to exercise dose, several epidemiologic studies report that the benefits of exercise on breast cancer recurrence and mortality only appear when women engage in rather high amounts of physical activity, equivalent to 3 hours or more per week of moderate to vigorous physical activity, or twice the level of current public health recommendations (24). Kang recently concluded from a meta-analysis of controlled exercise trials ($n = 14$) that examined one or more biomarkers of cancer progression that the mode, volume, and length of exercise programs varied widely leaving little information that would be useful for prescribing an effective exercise program that could alter biologic pathways of cancer progression.

We had the opportunity to analyze biological specimen data from our 3 year-long randomized controlled resistance training trials to address several unanswered questions about the effectiveness of exercise to reduce biological markers of breast cancer progression. The aims of the proposed study were to: (i) determine whether or not resistance training reduces different biomarkers of cancer progression in postmenopausal breast cancer survivors; (ii) determine the influence of changes in weight and/or body composition and changes in muscle strength on biomarkers; and (iii) explore additional potential effect modifiers on the efficacy of exercise.

Materials and Methods

Design

We performed a secondary data analysis on stored samples from three separate randomized, controlled trials testing the effects of resistance training in breast cancer survivors at risk of poor musculoskeletal health and functional decline related to cancer treatment. Two of the three studies were two group designs with women randomized to resistance training or stretching control groups (NCT00659906, NCT00591747). The third study was a comparison of resistance to aerobic exercise versus a stretching control group (NCT00665080), but only data from the resistance and stretching control groups were used for this analysis. Eligibility for the original trials included diagnosis of stage 0–IIIc breast cancer, postmenopausal status, <twice weekly resistance training within the last month, ≥ 1 year past chemotherapy and/or radiotherapy, and physician clearance to participate in moderate-intensity exercise. Studies were approved by the OHSU Institutional Review Board and samples were stored in an approved biorepository for future analysis. In every study, providing blood samples was an optional part of participation.

Interventions

Details for study interventions have been described previously (25–28), but are briefly summarized here. Participants in both groups were prescribed an exercise program consisting of two 1-hour supervised classes and one 45-minute home-based session per week for 12 months. Our resistance training programs were based on our prior intervention in women without cancer (29) and complied with the American College of Sports Medicine recommendations for 2 to 3 sets of multiple- and single-joint exercises at a weight that can be done for 8 to 12 repetitions ($\sim 60\%$ – 80% of 1-repetition max; ref. 30). Free weights were used

to apply resistance, dumbbells for upper body, weighted vests for lower body, and a barbell for one combined upper + lower body exercise. Participants in the control group performed a series of whole-body stretching and relaxation exercises in a seated or lying position to minimize weight-bearing forces and energy expenditure. Compared with controls, resistance training resulted in significant increases in lower and upper body strength, measured by one-repetition maximum leg and bench press tests, in women assigned to the resistance training group in each study population (25–28). Average attendance at exercise classes across the three studies and groups was 75%, comparable with similar length studies in breast cancer survivors (31, 32).

Sample collection and analysis

A total of 254 women participated in the three studies with 215 participants (87%) providing blood samples at baseline, 6, and 12 months (Supplementary Fig. S1). Women consenting to blood samples did not differ from women who opted out on baseline characteristics. Participants were fasted for 12+ hours and abstained from smoking, drinking alcohol or caffeinated beverages, and strenuous exercise for ≥ 12 hours prior to blood draws. Blood samples were centrifuged and the serum layer was removed, then aliquoted into 1 mL vials and stored at -70°C .

Measures

Serum biomarkers. Serum levels of IGF-1, IGFBP1, IGFBP3, IL1 β , IL6, TNF α , leptin, adiponectin, SAA, and CRP were measured in duplicate using a magnetic bead-based immunofluorescence assay (Luminex Inc.) using commercially available kits from Millipore Corp. Data were collected and analyzed using the Luminex-200 system Version IS (Luminex). A five-parameter regression formula was used to calculate the sample concentrations from the standard curves. Interassay and intra-assay coefficient of variation (CV) for IGF-1, IGFBP1, IGFBP3, IL1 β , IL6, TNF α , leptin, and adiponectin were $<10\%$ and $<15\%$, respectively. Interassay and intra-assay CVs for SAA, and CRP were $<15\%$ and $<20\%$, respectively. To minimize lot-to-lot and user-to-user variation in analyte levels determined by bead-based assays, sera were batch analyzed by the same technicians using kits with the same lot number. Serum insulin levels were measured by chemoluminescent assay with interassay and intra-assay CVs of $<7\%$.

Body composition. Body composition was assessed by dual energy x-ray absorptiometry (DXA; Hologic QDR Discovery Wi, APEX software v4.0), which allows for calculation of body mass, fat mass, and lean mass in the total body. All scans were performed and analyzed by personnel trained in densitometry and blinded to group assignment. CVs for these measures range from 1% to 2%.

Other potential confounders. Demographic, clinical history, and medication use, including the use of antiestrogen hormone therapy for breast cancer (i.e., selective estrogen receptor modulator or aromatase inhibitor therapy) and the use of medications known to affect inflammatory markers (i.e., NSAIDs or statins) was obtained by self-report at baseline. To consider whether energy balance changed across the study period, we measured self-report physical activity in the last 4 weeks with the Community Health Activity Model Program for Seniors (CHAMPS) questionnaire for older adults (kcal/week in moderate-vigorous intensity activities; ref. 33) and self-report

Winters-Stone et al.

total energy intake (kcal/week) using the 2005 Block Food Frequency Questionnaire (34).

Sample size and analysis

Power analyses based on common assumptions of repeated measures ANOVA suggested that a sample size of approximately 100 patients per group would allow the detection of small group \times time interaction effects (Cohen $d = 0.20$). Published literature suggested that changes in metabolic markers and adipocytokines frequently exceed the small effect size range (23, 35–37). Standard t tests and χ^2 tests were used to compare clinical and demographic variables between the resistance and control groups. The primary analyses were conducted using a linear mixed effects modeling approach implemented in the nlme package for the R statistical computing environment (38, 39). The base model included fixed effects for group (resistance vs. control), time (baseline, 6, and 12 months), and the group \times time interaction to test whether the change in outcomes across time differed between the training groups. All biomarkers were log transformed with base e before being used in the models to improve normality of their distributions, and we report modeled intercepts (adjusted means at baseline) and slopes (transformed to reflect percentage change over one year) for each group to facilitate interpretation of the results. Slopes for the body composition and energy expenditure outcome models reflect change over one year in the raw metric of each variable. Age, time since diagnosis, antiestrogen hormone therapy, were included as covariates in all mixed effects models to control for their potential influence on participant tolerance and response to exercise (40, 41). NSAID and statin use added as controls in mixed effects models when biomarkers were the outcome measure because of their potential influence on inflammatory and insulin pathways (42, 43). We also assessed intervention effects stratified by changes in strength and body composition using changes in 1-RM leg press strength ($<10\%$ increase vs. $\leq 10\%$ increase) as a marker of training compliance and changes in weight (≥ 2 kg weight loss vs. gain) and fat mass (≥ 1 kg fat loss vs. gain) with all dependent variables. Cut-off values for stratification variables were selected on the basis of the known measurement error 1-RM testing (27, 44, 45) and DXA (46). To better understand participant characteristics that might modify the effectiveness of exercise on biomarkers that changed between groups across the intervention period, we performed additional stratification by age (<60 years, ≥ 60 years), BMI (<30 kg/m², ≥ 30 kg/m²), baseline CRP (<3.0 mg/L, ≥ 3.0 mg/L), NSAID use (yes/no), and statin use (yes/no; ref. 47). For all stratification analyses, outcomes were only stratified in the resistance training group and compared with the full control group. Alpha was set at $P = 0.05$ for all analyses.

Results

Study participant characteristics

There was no significant difference between the resistance exercise and control stretching groups on any demographic variables (Table 1). Participants in both groups were predominantly white, married or partnered, and college educated with a mean age of 59 years and mean BMI in the overweight category. The majority of women were diagnosed with breast cancer about 5 years prior to enrollment, and most women had stage I/II disease.

Table 1. Baseline characteristics of the combined sample

Characteristics	Control	Resistance	P
	(n = 106)	(n = 109)	
	M (SD) or %	M (SD) or %	
Age (years)	59.3 (11.6)	59.8 (11.4)	0.743
Race (%)			0.878 ^a
White	95.2	96.3	
Black	1.9	1.8	
Other	2.9	1.8	
Non-Hispanic	99.0	99.1	1.000
Married/partnered (%)	61.0	62.4	0.940
College education or higher (%)	62.2	61.2	0.990
BMI (kg/m ²)	28.5 (5.3)	27.9 (5.5)	0.404
Physical activity (kcal/day)			
Moderate intensity exercise	203 (190)	193 (232)	0.714
Energy intake (kcal/day)	1,379 (430)	1,537 (606)	0.031
Breast cancer stage (%)			
Stage 0	6.0	4.7	
Stage I	39.0	38.3	0.750
Stage II	44.0	49.5	
Stage III	11.0	7.5	
Time since diagnosis (mos.)	58.3 (38.2)	56.6 (42.6)	0.764
Received chemotherapy (%)	68.9	69.7	1.000
Received radiotherapy (%)	78.3	82.6	0.537
NSAID user (%)	16.7	20.2	0.595
Statin user (%)	19.6	15.6	0.559

^aFisher exact test used due to small cell count.

Main intervention effects on biomarkers, body composition, and energy balance

Across the year-long intervention, women in the resistance training groups experienced modest decreases (4%) in CRP levels, which were significantly different from substantial increases (+57%) among controls ($P = 0.045$). There were no significant group differences between resistance and control groups for other biomarkers (Table 2). Changes in body composition and weight between groups were in the expected direction where women in the control group gained weight and fat mass while exercising women maintained; however, group differences were not significant. Women who resistance trained reported less of a decrease in overall physical activity energy expenditure (-244 kcal/week) and an increase in moderate to vigorous intensity physical activity ($+120$ kcal/week) compared with decreases over time reported for overall (-843 kcal/week) and moderate vigorous intensity (-350 kcal/week) physical activity measures in controls (P for interaction $P = 0.08$ and $P = 0.04$, respectively; Table 3). To ensure findings were not affected by study group or energy balance at baseline, we reran analyses including each factor as a covariate, and results were unaltered.

Intervention effects stratified by changes in muscle strength

To explore whether or not changes in biomarkers depending upon whether or not women responded to the resistance training intervention, we stratified analysis by changes in muscle strength (Table 4). Women who gained strength did not differ from women who did not on baseline characteristics. Compared with all controls, women who got stronger decreased their CRP levels by 37% compared with a 57% increase in controls ($P = 0.004$). No other biomarker differed between women in the exercise group who increased strength and controls. However, among women in the exercise group who did not improve their strength, IL β and IL6 increased compared with small decreases in controls ($P = 0.05$ and $P = 0.049$, respectively).

Table 2. Adjusted mean^a at baseline^a and percent change in biomarkers with 95% CI for stretching control and resistance training and groups

Biomarker	Control (n = 106)		Resistance (n = 109)		P
	Mean (95% CI)	% Change over 1 year	Mean (95% CI)	% Change over 1 year	
CRP ^a	1.2 (0.7-2.0)	57.1 (10.5-123.2)	1.3 (0.5-3.5)	-4.0 (-58.3-120.9)	0.045
IL1 β	0.3 (0.2-0.4)	-5.9 (-17.8-7.8)	0.3 (0.1-0.5)	1.8 (-26.5-40.9)	0.420
IL6	1.9 (1.3-2.7)	-4.5 (-27.0-24.8)	2.0 (0.9-4.3)	-8.2 (-51.7-74.3)	0.836
IL8	5.9 (5.0-6.9)	-9.5 (-18.1-0.0)	5.9 (4.2-8.1)	-2.8 (-23.5-23.4)	0.314
TNF α	7.0 (5.8-8.4)	-6.4 (-16.8-5.2)	7.3 (5.0-10.5)	-4.5 (-27.9-26.4)	0.808
Adiponectin	25.9 (22.0-30.5)	0.8 (-10.0-12.8)	27.8 (20.1-38.5)	-7.8 (-29.5-20.7)	0.266
Leptin	11.6 (8.7-15.3)	8.5 (-5.4-24.4)	9.9 (5.7-17.2)	3.4 (-25.2-43.0)	0.611
SAA	7.0 (5.3-9.2)	26.0 (3.0-54.0)	8.9 (5.1-15.4)	0.2 (-37.8-61.3)	0.102
IGF-1	116.8 (106.8-127.7)	0.8 (-4.7-6.6)	123.0 (102.7-147.3)	-0.3 (-12.8-14.1)	0.791
IGF-BP1	3.1 (2.5-3.9)	-4.9 (-18.4-10.8)	3.1 (2.0-4.8)	-2.0 (-31.8-40.7)	0.781
IGF-BP3	566.0 (519.3-616.8)	-1.5 (-5.8-2.9)	540.7 (456.9-639.9)	-0.2 (-10.1-10.8)	0.666
Insulin	5.8 (4.8-7.1)	-17.2 (-28.9 to -3.5)	6.4 (4.3-9.6)	-24.7 (-47.9-8.7)	0.383

Abbreviation: CI, confidence interval.

^aOne outlier removed.

*Geometric mean calculated from mixed-effects model with age, time since diagnosis, and antihormone therapy, NSAID, and statin use as covariates.

Intervention effects stratified by weight loss or gain

Although not the primary focus of this analysis, we initially examined whether or not changes in biomarkers were influenced by changes in body composition among the whole sample to confirm that these relationships existed and observed significant relationships between loss of total fat and trunk fat and several markers (Supplementary Table S1). Next, we sought to explore whether or not the influence of resistance training on biomarkers differed between women who lost or gained body weight or fat using stratified analyses (Table 5; Supplementary Tables S2 and S3). Compared with controls, women in the resistance training group who lost weight had significant decreases in CRP (31%; $P = 0.046$), leptin (30%; $P = 0.0001$), and SAA (28%; $P = 0.029$). Among women in the resistance training group who gained weight leptin increased more than increases in controls ($P = 0.0002$). For insulin pathway proteins, women who lost weight during resistance training had a 37% increase in IGF-BP1 that differed significantly from a 5% decrease in controls ($P = 0.036$). Women who lost weight did not differ from women who gained on baseline characteristics. For women in the resistance training group, leptin significantly decreased among those who lost total body or trunk fat mass ($P < 0.001$), and SAA decreased for women who lost trunk fat mass ($P < 0.015$). There were no significant findings stratifying by changes in lean mass.

Intervention effects on CRP stratified by baseline characteristics and medication use

As CRP was the only biomarker to show a reduction from resistance exercise in the full analysis, we only performed additional stratification analyses on this outcome (Table 6). Among

women who resistance trained, changes in CRP were significantly different from controls and in a favorable direction among women who had a baseline BMI ≥ 30 kg/m² ($P = 0.046$), low baseline CRP ($P = 0.014$), or who were not taking NSAIDs at study entry ($P = 0.029$). Group differences were independent of statin use and age.

Discussion

Our secondary data analysis of three year-long studies found that resistance training prevented increases in a general marker of inflammation, CRP, compared with controls that did seated stretching exercise. Training appeared to be more effective at limiting inflammation among women who were heavier, had less inflammation, and did not use NSAIDs at the start of training. We also examined other conditions that may influence the effectiveness of exercise. Resistance training significantly reduced CRP when women achieved at least a 10% gain in strength, which may indicate better compliance to training. Weight/fat loss during resistance training may have led to better outcomes, where weight/fat loss led to reductions in additional inflammatory markers, that is, SAA and leptin, and increases in IGF-BP1 that differed from controls.

We are the first to report that resistance training prevented increases in a serum marker of inflammation in postmenopausal breast cancer survivors. To our knowledge, only two other trials have examined the effects of resistance training on inflammatory markers. Hagstrom reported that a 16-week supervised resistance training program reduced natural killer and natural killer T-cell expression of TNF α in a small sample of breast cancer survivors ($n = 39$), but had no effect on CRP or other inflammatory markers (48). In contrast, Ergun reported no effect of a supervised 12-week

Table 3. Adjusted mean at baseline^a and mean change in biomarkers with 95% CI for stretching control and resistance training and groups

	Control (n = 106)		Resistance (n = 109)		P
	Mean (95% CI)	1-yr change (95% CI)	Mean (95% CI)	1-yr change (95% CI)	
Weight (kg)	78.3 (74.6-82.0)	1.0 (0.1-1.9)	76.1 (68.4-83.8)	0.6 (-1.6-2.7)	0.466
Lean mass (kg)	45.0 (43.5-46.5)	0.4 (0.1-0.7)	44.3 (41.3-47.4)	0.5 (-0.2-1.2)	0.787
Fat mass (kg)	31.9 (29.4-34.4)	0.4 (-0.3-1.1)	30.6 (35.5-35.8)	0.1 (-1.6-1.8)	0.525
Trunk fat mass (kg)	15.9 (14.3-17.4)	0.3 (-0.1-0.8)	15.0 (11.8-18.1)	0.0 (-1.0-1.0)	0.268
Body fat (%)	40.6 (39.0-42.2)	0.2 (-0.3-0.7)	39.8 (36.5-43.1)	-0.2 (-1.4-0.9)	0.237
Physical activity (kcal/day)	193 (140-245)	20 (-27-68)	207 (96-318)	93 (-20-206)	0.030
Energy Intake (kcal/day)	1,486 (1,359-1,613)	-151 (-235 to -66)	1,354 (1,089-1,619)	-19 (-221-183)	0.028

Abbreviation: CI, confidence interval.

^aMean calculated from mixed effects model with age, time since diagnosis, and antihormone therapy use as covariates.

Table 4. Changes in biomarkers stratified by $\leq 10\%$ increase vs. $>10\%$ increase in maximal leg strength among women in the resistance training groups and compared with controls

	Control		$<10\%$ \uparrow strength		P	Control		$>10\%$ \uparrow strength		P
	n	% Change	n	% Change		n	% Change	n	% Change	
CRP	77	57.3	31	36.6	0.661	77	57.1	44	-31.7	0.004
IL1 β	100	-5.4	30	24.6	0.050	100	-5.7	49	-12.9	0.486
IL6	100	-6.2	30	60.6	0.049	100	-3.6	49	-30.5	0.123
IL8	100	-9.3	30	-2.6	0.480	100	-9.5	49	-3.8	0.483
TNF α	100	-6.9	30	2.7	0.432	100	-6.8	49	-8.4	0.863
Adiponectin	92	1.2	31	-10.3	0.253	92	1.0	49	-7.7	0.330
Leptin	77	8.4	31	0.6	0.543	77	8.1	44	3.9	0.688
SAA	65	25.7	29	0.5	0.221	65	25.9	43	-0.6	0.163
IGF-1	102	0.7	33	-1.1	0.755	102	0.9	50	1.0	0.983
IGF-BP1	77	-4.7	31	-1.8	0.815	77	-4.6	45	0.7	0.672
IGF-BP3	77	-1.5	31	0.1	0.668	77	-1.6	45	-1.3	0.938
Insulin	102	-17.1	32	-17.5	0.977	102	-17.5	50	-28.8	0.264

resistance training program on serum markers of inflammation in 60 breast cancer survivors (49). In their meta-analysis, Kang reported a nonsignificant trend for a positive effect of exercise, in general, on lowering CRP but noted that studies were few ($n = 4$) and sample sizes were small (17). By combining samples from three of our trials that used the same type of resistance training program, we were able to overcome limitations of sample size in individual studies and of inconsistency in training modes in meta-analyses. Our training program was also among the longest of any trial of exercise and inflammation in breast cancer survivors; thus, our findings provide robust data on the long-term benefits of exercise, which support epidemiologic observations that exercise patterns over the past year were associated with breast cancer recurrence and mortality (24). A recent meta-analysis of CRP in breast cancer survivors found CRP to be a strong prognostic indicator of breast cancer survival (6), while the WHEL trial reported that a 1-unit increase in lnCRP levels translated to a 21% increase in all-cause mortality and an 18% increase in breast cancer-specific mortality (5). The between group difference over one year in our study was 0.5-unit lnCRP; thus, it is possible that if these changes are sustained over time that resistance training could protect against increases in recurrence and mortality risk.

In our larger sample, the impact of our intervention to prevent increases in CRP may be related to differences in energy expenditure between groups. Women in our control group were assigned to a supervised stretching program, and an unintentional outcome in that group was a decrease in self-reported moderate to vigorous physical activity, that might occur if women substituted

stretching for other types of exercise. Decreasing physical activity may have led to increases in CRP that was prevented when women engaged in regular resistance training. To decrease inflammation, though, compliance to training may be more important than keeping regularly active. A recent review in noncancer populations reported that resistance training may be particularly effective at reducing CRP levels in obese individuals, older adults, and women when training programs are longer than 16 weeks and intense enough to build strength (50). In stratified analysis of our yearlong program, women who increased their strength by 10% or more reduced CRP by 31% compared with women who improved less. We also found better reductions in CRP among obese (BMI > 30 kg/m²) versus nonobese women ($P < 0.05$) and a trend among older (60+ years) versus younger women ($P = 0.09$). Our results are similar to a training study in noncancer patients, which reported that resistance, but not aerobic training, reduced serum CRP levels and that reductions in CRP were correlated with increases strength improvements but not with changes in lean body mass, which were small (51). Secondary analyses of individual resistance exercise trials suggest that clinical, behavioral, and social factors may influence adherence to training (52, 53); thus, inclusion of behavioral approaches to improve adherence and compliance to resistance exercise among breast cancer survivors should be a consideration in future intervention trials.

Although exercise may have a direct effect on markers of cancer progression, weight/fat loss may also be a likely mechanism for

Table 5. Changes in biomarkers stratified by ≥ 2 kg weight loss vs. >2 kg weight gain among women in the resistance training groups and compared with controls

	Control		Weight loss		P	Control		Weight gain		P
	n	% Change	n	% Change		n	% Change	n	% Change	
CRP	77	56.4	17	-31.1	0.046	77	56.4	19	11.4	0.364
IL1 β	100	-5.5	16	-6.0	0.978	100	-5.7	22	13.4	0.245
IL6	100	-4.4	16	-21.4	0.569	100	-4.3	22	-3.5	0.979
IL8	100	-9.6	16	-3.2	0.631	100	-9.2	22	-3.7	0.611
TNF α	100	-7.0	16	-1.3	0.723	100	-7.2	22	-8.4	0.934
Adiponectin	92	1.3	17	6.0	0.718	92	1.5	22	-3.8	0.626
Leptin	77	8.3	17	-29.9	0.000	77	8.0	19	72.8	0.000
SAA	65	25.7	14	-27.8	0.029	65	26.0	18	19.0	0.797
IGF-1	102	1.1	17	0.3	0.919	102	0.8	23	2.6	0.801
IGF-BP1	77	-4.9	17	37.2	0.036	77	-4.6	19	-13.3	0.553
IGF-BP3	77	-1.6	17	-0.5	0.819	77	-1.5	19	-3.9	0.645
Insulin	102	-17.5	17	-34.2	0.190	102	-17.0	23	-34.7	0.209

Table 6. Changes in CRP stratified by select baseline characteristics

	Control (n = 106)		Resistance (n = 109)		P
	n	% Change	n	% Change	
Age (years)					
<60	41	60.6	39	15.4	0.384
≥60	36	49.9	48	-15.3	0.095
BMI (kg/m ²)					
<30	53	49.6	65	10.6	0.320
≥30	24	62.3	22	-30.3	0.047
Baseline CRP (mg/dL)					
<3	55	138.0	53	23.1	0.014
≥3	19	-52.7	30	-45.8	0.775
NSAIDs					
Nonuser	61	51.6	68	42.6	0.913
User	16	60.8	19	-12.6	0.029
Statin					
Nonuser	62	21.8	73	-9.2	0.070
User	15	68.2	14	-1.1	0.557

reducing mortality and recurrence risk (4). In our stratified analysis comparing women who lost weight/fat during resistance training and to controls, group differences in CRP remained, and additional benefits were found for leptin, SAA, and IGF-BP1, while women who resistance trained but gained weight/fat experienced unfavorable increases in leptin. Whether or not exercise effects on adipocytokines are conditional upon weight/fat loss is not clear. Ligibel and colleagues reported no changes in adipocytokines after a 16-week aerobic + resistance training that did not shift body weight or composition (54), while Rogers and colleagues reported reductions in leptin following a similar 12-week program despite no effect on body composition (55). Alterations in the insulin pathway that serve to increase bioavailable insulin have been associated with an increased risk of breast cancer recurrence and mortality (56). When stratifying by weight change, we also found that resistance training plus weight loss increased levels of IGFBP1, but not other markers. IGF-BP1 may be a small but significant regulator of IGF-1 bioactivity, and levels of IGFBP-1 are inversely associated with breast cancer risk (57) and are predictive of distant recurrence and death in breast cancer survivors (58). IGFBP-1 is also correlated with BMI and diet, particularly excess intake of fats and carbohydrates (58). Given our findings, future studies should consider the potential combined effects of resistance training and diet modification on biomarkers and recurrence risk.

To our knowledge, we are the first study to combine data from three samples of breast cancer survivors participating in a similar resistance training intervention to investigate the effects of strength training on biomarkers associated with cancer progression. By combining datasets from three similar trials, we could overcome the limitation of small sample sizes that have limited other training studies (17). As our participants were exposed to the same intervention across studies, we can more definitively attribute changes in biomarkers to a specific training modality, for example, resistance exercise, that we have shown already has significant benefits on musculoskeletal health to reduce risk factors for fractures and future disability (25–28). We also included different types of biomarkers associated with breast cancer recurrence; thus, we were less likely to miss a potential benefit of training on the insulin and/or inflammatory pathways. We were also among the first to investigate factors that might influence the biomarker response to training. Although other studies outside of

cancer have examined potential modifiers of biomarker responses (47, 59), this approach has been sporadically included in studies in breast cancer survivors. Although our study has many strengths, it also is limited by the fact that our original studies were not designed for weight/fat loss nor did they target women with unfavorable inflammatory or insulin profiles. In our cohort, serum CRP and insulin levels approximated those found in the general U.S. population (60, 61). Population norms for the remaining analytes have not been established, and therefore, we are unable to compare their levels to those in the general population. Thus, the lack of an intervention effect for these analytes may indeed simply reflect that their levels were not unfavorable at baseline. Studies that intentionally aim to alter weight during resistance training among at-risk women may be better able to investigate the independent and combined effects of weight loss plus exercise to alter markers of cancer progression.

Using a secondary data analyses approach of multiple resistance training trials, we found that resistance training may lower systemic inflammation and favorably alter insulin pathways in breast cancer survivors, but also that the effectiveness of resistance training may be optimized under certain conditions. Specifically, we found that a modest degree of strength gains and a mild amount of weight/fat loss led to optimal outcomes. Although controlled trials of resistance training with survival endpoints do not exist, our findings suggest that resistance training programs that improve musculoskeletal health may also favorably alter pathways of cancer progression. Our findings also suggest that along with resistance training and concomitant weight loss may be an important component of a lifestyle approach to improving breast cancer survival.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: K.M. Winters-Stone, L.J. Wood

Development of methodology: K.M. Winters-Stone

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.M. Winters-Stone, L.J. Wood

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.M. Winters-Stone, S. Stoyles, N.F. Dieckmann

Writing, review, and/or revision of the manuscript: K.M. Winters-Stone, L.J. Wood, S. Stoyles, N.F. Dieckmann

Winters-Stone et al.

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Stoyles
Study supervision: K.M. Winters-Stone

Acknowledgments

This work was funded by NIH grant 1R21CA164661. K.M. Winters-Stone is partially supported by NIH grants 1R01CA163474, 1R21HL115251, and P30CA069533. L.J. Wood is partially supported by NINR R01NR012479.

References

- Ibrahim EM, Al-Homaidh A. Physical activity and survival after breast cancer diagnosis: meta-analysis of published studies. *Med Oncol* 2011; 28:753–65.
- McTiernan A. Mechanisms linking physical activity with cancer. *Nat Rev Cancer* 2008;8:205–11.
- Neilson HK, Friedenreich CM, Brockton NT, Millikan RC. Physical activity and postmenopausal breast cancer: proposed biologic mechanisms and areas for future research. *Cancer Epidemiol Biomarkers Prev* 2009;18:11–27.
- Dieli-Conwright CM, Lee K, Kiwata JL. Reducing the risk of breast cancer recurrence: an evaluation of the effects and mechanisms of diet and exercise. *Curr Breast Cancer Rep* 2016;8:139–50.
- Villaseñor A, Flatt SW, Marinac C, Natarajan L, Pierce JP, Patterson RE. Postdiagnosis C-reactive protein and breast cancer survivorship: findings from the WHEL study. *Cancer Epidemiol Biomarkers Prev* 2014; 23:189–99.
- Han Y, Mao F, Wu Y, Fu X, Zhu X, Zhou S, et al. Prognostic role of C-reactive protein in breast cancer: a systematic review and meta-analysis. *Int J Biol Markers* 2011;26:209–15.
- Crespi E, Bottai G, Santarpia L. Role of inflammation in obesity-related breast cancer. *Curr Opin Pharmacol* 2016;31:114–22.
- Hartog H, Boezen HM, de Jong MM, Schaapveld M, Wesseling J, van der Graaf WT. Prognostic value of insulin-like growth factor 1 and insulin-like growth factor binding protein 3 blood levels in breast cancer. *Breast* 2013;22:1155–60.
- Duggan C, Wang C-Y, Neuhaus ML, Xiao L, Smith AW, Reding KW, et al. Associations of insulin-like growth factor and insulin-like growth factor binding protein-3 with mortality in women with breast cancer. *Int J Cancer* 2013;132:1191–200.
- Coughlin SS, Smith SA. The insulin-like growth factor axis, adipokines, physical activity, and obesity in relation to breast cancer incidence and recurrence. *Cancer Clin Oncol* 2015;4:24–31.
- Christopoulos PF, Msaouel P, Koutsilieris M. The role of the insulin-like growth factor-1 system in breast cancer. *Mol Cancer* 2015;14:43.
- Walsh NP, Gleeson M, Shephard RJ, Woods JA, Bishop NC, Fleshner M, et al. Position statement. Part one: immune function and exercise. *Exerc Immunol Rev* 2011;17:6–63.
- Nimmo MA, Leggate M, Viana JL, King JA. The effect of physical activity on mediators of inflammation. *Diabetes Obes Metab* 2013;15(s3):51–60.
- Devin JL, Bolam KA, Jenkins DG, Skinner TL. The influence of exercise on the insulin-like growth factor axis in oncology: physiological basis, current and future perspectives. *Cancer Epidemiol Biomarkers Prev* 2015;25:239–49.
- Orenstein MR, Friedenreich CM. Review of physical activity and the IGF family. *J Phys Act Health* 2004;1:291–320.
- Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst* 2012;104:815–40.
- Kang D-W, Lee J, Suh S-H, Ligibel J, Courneya KS, Jeon JY. Effects of exercise on insulin, IGF axis, adipocytokines, and inflammatory markers in breast cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2017;26:355–65.
- Meneses-Echavez JF, Correa-Bautista JE, Gonzalez-Jimenez E, Schmidt Rio-Valle J, Elkins MR, Lobelo F, et al. The effect of exercise training on mediators of inflammation in breast cancer survivors: a systematic review with meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2016;25: 1009–17.
- Meneses-Echavez JF, Jiménez EG, Río-Valle JS, Correa-Bautista JE, Izquierdo M, Ramírez-Vélez R. The insulin-like growth factor system is modulated by exercise in breast cancer survivors: a systematic review and meta-analysis. *BMC Cancer* 2016;16:682.
- Alfano CM, Bluethmann SM, Tesaro G, Perna F, Agurs-Collins T, Elena JW, et al. NCI funding trends and priorities in physical activity and energy balance research among cancer survivors. *J Natl Cancer Inst* 2015;108:pii: djv285.
- Martins RA, Neves AP, Coelho-Silva MJ, Verissimo MT, Teixeira AM. The effect of aerobic versus strength-based training on high-sensitivity C-reactive protein in older adults. *Eur J Appl Physiol* 2010;110:161–9.
- Vieira VJ, Hu L, Valentine RJ, McAuley E, Evans EM, Baynard T, et al. Reduction in trunk fat predicts cardiovascular exercise training-related reductions in C-reactive protein. *Brain Behav Immun* 2009;23:485–91.
- Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women. *JAMA* 2003;289:1799–804.
- Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA* 2005;293:2479–86.
- Winters-Stone K, Dobek J, Nail L, Bennett JA, Naik A, Schwartz A. Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors: a randomized controlled trial. *Breast Cancer Res Treat* 2011;27:447–56.
- Winters-Stone K, Dobek J, Nail L, Bennett JA, Naik A, Schwartz A. Comparison of aerobic to resistance exercise in older breast cancer survivors: preliminary findings from a one-year RCT. *Med Sci Sports Exerc* 2011;43 (Suppl 1):11.
- Winters-Stone KM, Dobek J, Bennett JA, Nail LM, Leo MC, Schwartz A. The effect of resistance training on muscle strength and physical function in older, postmenopausal breast cancer survivors: a randomized controlled trial. *J Cancer Surviv* 2012;6:189–99.
- Winters-Stone KM, Dobek J, Nail LM, Bennett JA, Leo MC, Torgrimson-Ojerio B, et al. Impact + resistance training improves bone health and body composition in prematurely menopausal breast cancer survivors: a randomized controlled trial. *Osteoporos Int* 2013;24:1637–46.
- Winters KM, Snow CM. Detraining reverses positive effects of exercise on the musculoskeletal system in premenopausal women. *J Bone Miner Res* 2000;15:2495–503.
- Kraemer WJ, Adams K, Cafarelli E, Dudley GA, Dooly C, Feigenbaum MS, et al. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2002;34:364–80.
- Twiss JJ, Waltman NL, Berg K, Ott CD, Gross GJ, Lindsey AM. An exercise intervention for breast cancer survivors with bone loss. *J Nurs Scholarsh* 2009;41:20–7.
- Schmitz KH, Ahmed RL, Troxel AB, Chevile A, Lewis-Grant L, Smith R, et al. Weight lifting for women at risk for breast cancer-related lymphedema. *JAMA* 2010;304:2699–705.
- Stewart A, Mills K, King A, Haskell W, Gillis D, Ritter P. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med Sci Sports Exerc* 2001;33:1126–41.
- Binkley N, Bilezikian JP, Kendler DL, Leib ES, Lewiecki EM, Petak SM. Summary of the International Society For Clinical Densitometry 2005 Position Development Conference. *J Bone Miner Res* 2007;22:643–5.
- Fairey AS, Courneya KS, Field CJ, Bell GJ, Jones LW, Mackey JR. Randomized controlled trial of exercise and blood immune function in postmenopausal breast cancer survivors. *J Appl Physiol* (1985) 2005;98:1534–40.
- Irwin ML, Varma K, Alvarez-Reeves M, Cadmus L, Wiley A, Chung GC. Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale exercise and survivorship study. *Cancer Epidemiol Biomarkers Prev* 2009;18:306–13.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received August 22, 2017; revised October 5, 2017; accepted November 2, 2017; published OnlineFirst November 15, 2017.

37. Schmitz KH, Ahmed RL, Hannan PJ, Yee D. Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. *Cancer Epidemiol Biomarkers Prev* 2005;14:1672–80.
38. Pinheiro J, Bates D, DebRoy S, Sarkar D, R Core Development Team. nlme: linear and nonlinear mixed effects models. Vienna, Austria: R Foundation for Statistical Computing; 2016.
39. R Core Development Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2016.
40. Winters-Stone K, Leo M, Schwartz A. Exercise effects on hip bone mineral density in older, postmenopausal breast cancer survivors are age dependent. *Arch Osteoporos* 2012;7:301–6.
41. Nyrop KA, Callahan LF, Rini C, Altpeter M, Hackney B, DePue A, et al. Aromatase inhibitor associated arthralgia: the importance of oncology provider-patient communication about side effects and potential management through physical activity. *Support Care Cancer* 2016;24:2643–50.
42. Prasad K. C-reactive protein (CRP)-lowering agents. *Cardiovasc Drug Rev* 2006;24:33–50.
43. Yoon SS, Dillon CF, Carroll M, Illoh K, Ostchega Y. Effects of statins on serum inflammatory markers: the U.S. National Health and Nutrition Examination Survey 1999–2004. *J Atheroscler Thromb* 2010;17:1176–82.
44. Phillips WT, Batterham AM, Valenzuela JE, Burkett LN. Reliability of maximal strength testing in older adults. *Arch Phys Med Rehabil* 2004;85:329–34.
45. Schroeder ET, Wang Y, Castaneda-Sceppa C, Cloutier G, Vallejo AF, Kawakubo M, et al. Reliability of maximal voluntary muscle strength and power testing in older men. *J Gerontol A Biol Sci Med Sci* 2007;62:543–9.
46. Bazzocchi A, Ponti F, Albisinni U, Battista G, Guglielmi G. DXA: technical aspects and application. *Eur J Radiol* 2016;85:1481–92.
47. Imayama I, Ulrich CM, Alfano CM, Wang C, Xiao L, Wener MH, et al. Effects of a caloric restriction weight loss diet and exercise on inflammatory biomarkers in overweight/obese postmenopausal women: a randomized controlled trial. *Cancer Res* 2012;72:2314–26.
48. Hagstrom AD, Marshall PW, Lonsdale C, Papalia S, Cheema BS, Toben C, et al. The effect of resistance training on markers of immune function and inflammation in previously sedentary women recovering from breast cancer: a randomized controlled trial. *Breast Cancer Res Treat* 2016;155:471–82.
49. Ergun M, Eyigor S, Karaca B, Kisim A, Uslu R. Effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in breast cancer patients. *Eur J Cancer Care* 2013;22:626–37.
50. de Salles BF, Simão R, Fleck SJ, Dias I, Kraemer-Aguiar LG, Bouskela E. Effects of resistance training on cytokines. *Int J Sports Med* 2010;31:441–50.
51. Donges C, Duffield R, Drinkwater E. Effects of resistance or aerobic exercise training on interleukin-6, C-reactive protein, and body composition. *Med Sci Sports Exerc* 2010;42:304–13.
52. Courmeya KS, Segal RJ, Reid RD, Jones LW, Malone SC, Venner PM, et al. Three independent factors predicted adherence in a randomized controlled trial of resistance exercise training among prostate cancer survivors. *J Clin Epidemiol* 2004;57:571–9.
53. Huberty JL, Vener J, Waltman N, Ott C, Twiss J, Gross G, et al. Development of an instrument to measure adherence to strength training in postmenopausal breast cancer survivors. *Oncol Nurs Forum* 2009;36:E266–73.
54. Ligibel JA, Giobbie-Hurder A, Olenczuk D, Campbell N, Salinardi T, Winer EP, et al. Impact of a mixed strength and endurance exercise intervention on levels of adiponectin, high molecular weight adiponectin and leptin in breast cancer survivors. *Cancer Causes Control* 2009;20:1523–8.
55. Rogers LQ, Fogleman A, Trammell R, Hopkins-Price P, Vicari S, Rao K, et al. Effects of a physical activity behavior change intervention on inflammation and related health outcomes in breast cancer survivors: pilot randomized trial. *Integr Cancer Ther* 2013;12:323–35.
56. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol* 2002;20:42–51.
57. Ng EH, Ji CY, Tan PH, Lin V, Soo KC, Lee KO. Altered serum levels of insulin-like growth-factor binding proteins in breast cancer patients. *Ann Surg Oncol* 1998;5:194–201.
58. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Hartwick W, et al. Insulin-like growth factor binding proteins 1 and 3 and breast cancer outcomes. *Breast Cancer Res Treat* 2002;74:65–76.
59. Mason C, Foster-Schubert KE, Imayama I, Kong A, Xiao L, Bain C, et al. Dietary weight loss and exercise effects on insulin resistance in postmenopausal women. *Am J Prev Med* 2011;41:366–75.
60. Woloshin S, Schwartz LM. Distribution of C-reactive protein values in the United States. *N Engl J Med* 2005;14:1611–3.
61. Harris MI CC, Gu K, Francis ME, Flegal K, Eberhardt MS. Higher fasting insulin but lower fasting C-peptide levels in African Americans in the US population. *Diabetes Metab Res Rev* 2002;18:149–55.

Cancer Epidemiology, Biomarkers & Prevention

The Effects of Resistance Exercise on Biomarkers of Breast Cancer Prognosis: A Pooled Analysis of Three Randomized Trials

Kerri M. Winters-Stone, Lisa J. Wood, Sydnee Stoyles, et al.

Cancer Epidemiol Biomarkers Prev 2018;27:146-153. Published OnlineFirst November 15, 2017.

Updated version Access the most recent version of this article at:
doi:[10.1158/1055-9965.EPI-17-0766](https://doi.org/10.1158/1055-9965.EPI-17-0766)

Supplementary Material Access the most recent supplemental material at:
<http://cebp.aacrjournals.org/content/suppl/2017/11/14/1055-9965.EPI-17-0766.DC1>

Cited articles This article cites 59 articles, 8 of which you can access for free at:
<http://cebp.aacrjournals.org/content/27/2/146.full#ref-list-1>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://cebp.aacrjournals.org/content/27/2/146>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.