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Research Article

Cancer Epidemiology, Biomarkers & Prevention

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

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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), IL1β, TNFα, 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 IL1β 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 TNFα, 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

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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 (~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, IGFPB1, IGFBP3, IL1β, IL6, TNFα, 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, IGFPB1, IGFBP3, IL1β, IL6, TNFα, 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

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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 × 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 × 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. ≤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/m^2, ≥30 kg/m^2), 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 ($n = 106$) M (SD) or %	Resistance ($n = 109$) M (SD) or %	*P*
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 (kcals/day)			
Moderate intensity exercise	203 (190)	193 (232)	0.714
Energy intake (kcals/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

[a]Fisher 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, ILβ and IL6 increased compared with small decreases in controls ($P = 0.05$ and $P = 0.049$, respectively).

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

	Control ($n = 106$)		Resistance ($n = 109$)		
Biomarker	**Mean (95% CI)**	**% Change over 1 year**	**Mean (95% CI)**	**% Change over 1 year**	***P***
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
IL1β	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
TNFα	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.

[a]One 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/m^2 ($P = 0.046$), 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 TNFα 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 ($n = 109$)		
	Mean (95% CI)	**1-yr change (95% CI)**	**Mean (95% CI)**	**1-yr change (95% CI)**	***P***
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.

[a]Mean calculated from mixed effects model with age, time since diagnosis, and antihormone therapy use as covariates.

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

	Control		<10% ↑strength			Control		>10% ↑strength		
	n	% Change	*n*	% Change	*P*	*n*	% Change	*n*	% Change	*P*
CRP	77	−57.3	31	36.6	0.661	77	57.1	44	−31.7	0.004
IL1β	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
TNFα	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/m^2) 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			Control		Weight gain		
	n	% Change	*n*	% Change	*P*	*n*	% Change	*n*	% Change	*P*
CRP	77	56.4	17	−31.1	0.046	77	56.4	19	11.4	0.364
IL1β	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
TNFα	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

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Table 6. Changes in CRP stratified by select baseline characteristics

	Control ($n = 106$)		Resistance ($n = 109$)		
	n	**% Change**	***n***	**% Change**	***P***
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

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

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

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