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Resistance Training Reduces Inflammation and Fatigue and Improves Physical Function in Older Breast Cancer Survivors

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Abstract

Objective—Resistance training (RT) reduces fatigue and improves physical function and quality of life (QOL) in breast cancer survivors (BCS). This may be related to reductions in systemic and tissue-specific inflammation. This pilot study examines the hypothesis that RT induces changes in systemic and tissue-specific inflammation that contribute to improvements in physical and behavioral function in postmenopausal BCS.

Methods—Eleven BCS (60±2 years old; BMI: 30±1 kg/m²; mean±SEM) underwent assessments of fatigue (Piper Fatigue Scale), physical function, QOL (SF-36), glucose and lipid metabolism, and systemic, skeletal muscle, and adipose tissue inflammation (N=9) before and after 16 wks of moderate intensity whole-body RT.

Results—Muscle strength improved by 25–30% (P<0.01), QOL by 10% (P=0.04), chair stand time by 15% (P=0.01), six-minute walk distance by 4% (P=0.03) and fatigue decreased by 58% (P<0.01), fasting insulin by 18% (P=0.04), and diastolic and systolic blood pressure by ~5% (P=0.04) following RT. BCS with the worst fatigue and QOL demonstrated the greatest improvements (absolute change vs. baseline: fatigue: $r=-0.95$, P<0.01; QOL: $r=-0.82$; P<0.01). RT was associated with a ~25–35% relative reduction in plasma and adipose tissue protein levels of pro-inflammatory interleukin (IL)-6sR, serum amyloid A, and tumor necrosis factor- α and 75% relative increase in muscle pro-proliferative, angiogenic IL-8 protein content by 75% (all P<0.05). BCS with the highest baseline pro-inflammatory cytokine levels had the greatest absolute reductions, and the change in muscle IL-8 correlated directly with improvements in leg press strength ($r=0.53$, P=0.04).

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Conclusions—These preliminary results suggest that a progressive RT program effectively lowers plasma and tissue-specific inflammation and that these changes are associated with reductions in fatigue and improved physical and behavioral function in postmenopausal BCS.

Keywords

resistance training; inflammation; breast cancer survivor; menopause

Introduction

The 10-year survival from breast cancer rose from 65% to 83% in the last 40 years,¹ indicating a prolonged life expectancy. However, most breast cancer survivors (BCS) do not fully recover their premorbid physical and behavioral function and many develop obesity and diabetes following treatment,² suggesting that other factors affect health and recovery. Chronic inflammation is a risk factor for metabolic diseases, and elevated cytokine levels may be one mechanism for fatigue, poor quality of life (QOL), and mobility dysfunction in postmenopausal BCS.³

There is emerging evidence supporting exercise as a non-pharmacological therapy to prevent cancer recurrence and obesity during cancer survivorship.⁴ It seems that interventions that include resistance training (RT) are more efficacious than aerobic exercise in reducing fatigue and improving strength in BCS.⁵ To date, most studies show that these responses do not appear to be mediated by changes in systemic inflammation following RT in BCS.^{6–8} However, this may be because the mechanisms regulating the clinical effects of systemic cytokines are tissue-specific such that interleukin (IL)-6 released by skeletal muscle is anti-inflammatory, whereas when secreted by adipose tissue is pro-inflammatory.^{9, 10} This study tests the hypothesis that RT induces tissue-specific and systemic changes in inflammation that contribute to the improvements in strength, physical and behavioral function in postmenopausal BCS. This would have important implications for attenuating further behavioral and physical-functional declines in older BCS.

Methods

Recruitment and Screening

Two hundred eighty non-smoking, postmenopausal women were recruited from Baltimore MD through local newspaper advertisements. Thirty-two generally healthy women (48–75 years old, no menses 12 months) who performed aerobic exercise <30 min 3×/wk, were novice to RT, and had completed treatment for stage I-III breast cancer 1 year prior qualified by phone screening and were enrolled. They provided written, informed consent to procedures approved by the IRB of the University of Maryland School of Medicine. Medical exam excluded women with recurrent or active cancer, unstable or painful lymphedema, poorly controlled hypertension or dyslipidemia, heart disease, liver, renal or hematological disease, anemia, orthopedic and/or medical conditions that would affect their ability to RT. Eight women were medically ineligible and four were not postmenopausal; thus, 20 BCS underwent baseline testing. Six women withdrew due to time constraints, one had recurrent breast cancer prior to completing baseline tests, and two were excluded due to non-

compliance. The data are reported from the 11 women who completed the intervention. All medications, including treatment with tamoxifen in one and aromatase inhibitors in eight remained constant.

Baseline and Post Testing

Research testing at each time point occurred across five visits that were separated by at least one day: 1) strength testing; 2) VO₂max; 3) body composition and physical function; 4) oral glucose tolerance test (OGTT) and questionnaires; and 5) tissue biopsies.

Body Composition—BMI was calculated as weight (kg) divided by height (m²). Total body fat (%) and fat-free mass (FFM) were measured by dual energy x-ray absorptiometry (GE Lunar iDXA, Madison, WI), and visceral and subcutaneous abdominal fat areas at L4–L5 and muscle area at the mid-thigh by computed tomography (Somatom Sensation 64 Scanner; Siemens, Fairfield, CT).¹¹

Strength, Physical Activity and Functional Tests—Chair stand time was the fastest time of three trials taken to rise five times from a sitting to a standing position. The six-minute walk distance (6MWD) was the distance walked quickly on a flat, hard surface in six minutes. Gait speed was calculated from a four-meter walk at self-selected walking speed. One-repetition maximum (1-RM) tests determined chest press, leg press, and leg extension strength on pneumatic RT equipment (Keiser, Fresno, CA) and VO₂max was measured using a graded treadmill test to maximal exertion as previously described.¹² Participants were instructed to continue to perform their usual physical activities outside of the prescribed RT. This was assessed by measuring average non-structured total daily physical activity using Actical accelerometers (Philips Respironics, Murrysville, Pennsylvania) worn for seven days at baseline and after RT.

Fatigue and Quality of Life—The revised Piper Fatigue Scale provided an estimate of fatigue with zero representing none, 1–3 mild, 4–6 moderate, and 7–10 severe fatigue.¹³ The 36-item Short Form Health Survey¹⁴ was used to calculate the two norm-based Physical (PCS) and Mental (MCS) Component Summary scales, with higher values representing better perceived health.

Metabolism and Inflammation—All metabolic assessments occurred after a 12 hr fast and began between 8:00 am – 9:00 am. Plasma glucose and insulin profiles during a two hr 75g OGTT and lipids were assessed as previously described.¹¹ Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated as [(fasting insulin (μU/ml) × fasting glucose [mmol/l])/22.5].¹⁵ Indirect calorimetry (COSMED; Rome, Italy) measured resting metabolic rate (RMR) while participants rested in bed quietly for 30 minutes in a thermo-neutral environment.

Nine BCS agreed to abdominal subcutaneous adipose tissue and vastus lateralis muscle biopsies under local lidocaine anesthesia at baseline and within 36–48 hrs after the last RT session. Adipose tissue was rinsed free of blood with saline and aliquots of 75 mg were incubated in one ml M199 containing 1% BSA at 55 oscillations/min in a 37°C water bath. At three hrs, incubation media were frozen at –70°C. Frozen muscle samples were

lyophilized for 48 hrs and microdissected free of obvious connective tissue. Five mgs of microdissected muscle was homogenized in 180 μ L cold cell lysis buffer containing protease inhibitors (Roche 11836170001), centrifuged at $10,000 \times g$ for 5 min at 4°C , and the supernatant's total protein measured (Coomassie Plus, Pierce). Total protein also was measured in the plasma and incubation media from adipose tissue. Two-hundred fifty μ g of total protein for fat and muscle and 1,000 μ g of total protein for plasma were added to Human Obesity Antibody Array membranes (abcam ab169819) and incubated overnight to measure plasma and tissue IL-1 β , IL-6, and its soluble receptor IL-6sR, IL-8, serum amyloid A (SAA), and tumor necrosis factor- α (TNF- α) and plasma C-reactive protein (CRP). Each membrane contained $\pm$ controls for normalization. Pre and post samples were run together on each plate, images exposed using a FluorChem M (ProteinSimple), and data analyzed using Image J software (NIH). The inter-assay coefficient of variation was 14%. Plasma CRP also was run in duplicate by ELISA using a electrochemiluminescent assay (V-PLEX Human CRP Kit, Meso Scale Diagnostics) to compare to standardized values ($>3 \mu\text{g/mL}$) for chronic inflammation.

Intervention

Progressive, moderate-intensity, whole-body muscle training was performed 3 $\times$ /wk for 16 wks in a research gymnasium supervised by an exercise physiologist to ensure they safely performed the prescribed RT intervention. This involved 15 contractions for two sets and then to exhaustion on the third set for the major muscle groups: leg and chest press, knee extension, leg curl, row, abdominal crunch, and bicep curl for a total duration of 40–45 min using Keiser equipment. Resistance was gradually increased by the exercise physiologist to account for strength gains and to maximize the intensity of the training when participants were able to complete 20 repetitions on the third set. The increase in weight was individualized based upon the muscle group and physical abilities of the participant. Participants were instructed not to change their dietary habits, which were assessed using pre- and post-intervention five-day food records and weekly weights.

Statistical Analyses

Wilcoxon signed-rank tests assessed changes in outcome variables and Spearman correlation coefficients assessed the relationships between variables of interest. Results are mean $\pm$ SEM, with a 2-tailed P-value of <0.05 set as significance. Data were analyzed using SPSS (IBM, Version 24, Armonk, New York).

Results

Participant Characteristics (Table 1)

The mean ($\pm$ SEM) age of the 11 BCS (7 White, 4 Black) was 60 ± 2 years old (range: 48–75 years). Mean time after the diagnosis of breast cancer was 10 ± 3 years. The majority of women were overweight or obese (BMI: $30\pm 1 \text{ kg/m}^2$; range 23–35 kg/m^2) and deconditioned (VO_2max : $24\pm 2 \text{ ml/kg/min}$).

Effects of RT on Body Composition, Strength, and Physical Function

The women attended >80% ($85\pm 1\%$) of prescribed RT sessions without any major adverse effects. RT was associated with an increase in mid-thigh muscle area of 10%, but no changes in body weight, BMI, % body fat, FFM, or visceral or subcutaneous abdominal fat areas (Table 1).

RT was associated with a 25–30% improvement in strength, a 15% decrease in chair stand time, and a 4% increase in 6MWD (Table 1). Those with the worst strength and physical function at baseline made the greatest improvements (change vs. baseline: knee extension 1-RM: $r=-0.76$; $P=0.03$, chair stand time: $r=-0.70$; $P=0.04$, 6MWD: $r=-0.50$, $P=0.04$), and BCS with the greatest reductions in chair stand time had the greatest gains in leg press ($r=-0.48$; $P=0.04$) and knee extension ($r=-0.59$; $P=0.03$) strength. VO_2max , daily activity counts, RMR, and dietary intake did not change after RT (Table 1).

Effects of RT on Fatigue and Quality of Life

The mean baseline Piper Fatigue Scale score of 4.5 ± 0.8 indicated moderate fatigue (three BCS showed severe, four moderate, three mild and one no fatigue). RT was associated with a 58% decrease in the Piper Fatigue Scale score to 1.9 ± 0.2 ($P<0.01$), and BCS with the highest baseline Piper Fatigue Scale score decreased the most ($r=-0.95$, $P<0.01$). None of the women had moderate or severe fatigue by the Piper Fatigue Scale following RT (82% reported mild and 18% reported no fatigue). The baseline MCS and PCS QOL scores were comparable to the U.S. adult referent population.¹⁴ RT was associated with an 8% improvement in the PCS score (50 ± 3 vs. 54 ± 2 ; $P=0.04$), but the MCS score did not change (54 ± 3 vs. 55 ± 3 ; $P=0.93$). Those with the lowest baseline PCS QOL scores increased the most ($r=-0.82$; $P<0.01$).

Effects of RT on Metabolism and Inflammation

Hypertension was treated in five women, hypercholesterolemia in three, and three women were insulin resistant ($\text{HOMA-IR} = 2.5$)¹⁶ at baseline. RT was associated with an 18% and reduction in fasting insulin ($P=0.04$) and a ~5% reduction in diastolic and systolic BP ($P=0.04$), but there were no changes in fasting and 2-hr glucose, HOMA-IR, or lipids.

Four of the women were chronically inflamed ($\text{CRP}>3 \mu\text{g/mL}$) at baseline by ELISA measured CRP. RT reduced plasma CRP comparable amounts measured by ELISA (pre vs. post: $3.0\pm 0.4 \mu\text{g/mL}$ vs. $2.2\pm 0.5 \mu\text{g/mL}$; $-27\pm 16\%$, $P=0.18$) or antibody array ($-28\pm 17\%$, $P=0.31$). RT decreased relative protein content of $\text{TNF-}\alpha$, IL-6sR, and SAA in plasma and adipose tissue secretions on average by ~25–35% (Figure 1), and the absolute changes were greatest in those with the highest baseline inflammatory protein concentrations (plasma: $\text{TNF-}\alpha$: $r=-0.52$; $P=0.04$, IL-6sR: $r=-0.77$; $P<0.01$, SAA: $r=-0.49$; $P=0.04$; adipose tissue secretions: $\text{TNF-}\alpha$: $r=-0.64$; $P=0.03$, IL-6sR: $r=-0.83$; $P<0.01$, SAA: $r=-0.63$; $P=0.04$). Skeletal muscle protein content of IL-8 increased on average $75\pm 29\%$ ($P=0.03$) and the absolute change correlated positively with increases in leg press strength ($r=0.53$, $P=0.04$). There were reductions in myokines IL-6 and SAA in 6 of 9 women, with an overall mean changes of -11% ($P=0.10$) and -18% ($P=0.12$), respectively. Changes in the other myokines were variable and did not approach significance (Figure 1).

Discussion

There is considerable evidence supporting the hypothesis that chronic inflammation is associated with fatigue, poorer QOL, and reduced physical function in BCS.^{3, 17} The results of this study show that a progressive, well-supervised RT program is associated with increased muscle mass, improved physical function and QOL, and reduced fatigue in postmenopausal BCS. The changes in inflammation with RT appear to be tissue-specific, with reductions in the pro-inflammatory cytokines TNF- α , IL-6sR, and SAA in both plasma and adipose tissue and increases in the pro-proliferative IL-8 in muscle that parallel the reductions in fatigue and improvements in physical function and behavioral profiles. The finding that the BCS with the highest cytokine levels and worst baseline psychological and physical function derive the greatest health benefits from RT suggests that there is potential for these improvements to occur across a broad range of physiological and psychological dysfunction in BCS.

Whereas other RT studies demonstrate variable effects on cytokines in BCS, most measured only plasma cytokines and there was concomitant weight loss, which obscured the independent effects of RT.⁷ Further, the finding that the largest reductions in systemic cytokines with RT are observed in more obese women^{18, 19} could explain the failure of RT to reduce plasma inflammation in lean and overweight middle-aged²⁰ and postmenopausal^{7, 21} BCS seen previously.

Adipose tissue produces both pro- and anti-inflammatory mediators that influence the regulation of metabolic, immune and regenerative processes. Pro-inflammatory adipokines increase with age and obesity and are associated with lower muscle mass and strength, physical disability, and worse metabolic health in older adults.²² The ability of RT to reduce adipokines and systemic cytokines could ameliorate the adverse effects of chronic inflammation, potentially prolonging functional independence and QOL in BCS.²³

Previous studies examining the effects of RT on pro-inflammatory cytokines in skeletal muscle show inconsistent results, reporting both increases^{24, 25} and decreases^{26, 27} across various populations of older adults. Some studies show reductions in pro-inflammatory markers with exercise training in adipose tissue, but not muscle²⁸, and vice versa.²⁵ These discrepancies may be attributed to differences in the population studied (i.e., age, hormonal status, and comorbidities), RT intensity and duration, and changes in body weight. The increase observed in the myokine IL-8 in this study, a chemotactic factor that stimulates angiogenesis,¹⁰ could have pro-proliferative effects to augment muscle protein synthesis as suggested by the direct relationship seen between increases in lower extremity strength and IL-8 levels, and studies that show RT increases systemic and muscle IL-8.²⁹

Strengths of this study are the high rate of compliance, stability of diet, weight and activity of the participants, and microdissection of muscle prior to cytokine measurement. Limitations include the small sample size and lack of follow-up, which should be considered in the design of future trials. The possibility of regression to the mean should be considered to avoid making incorrect inferences in the interpretation of these data. This limitation would have been avoided by randomization to a comparison group; nevertheless, the

magnitude of the physical and behavioral improvements observed in these BCS in response to a carefully supervised resistive exercise training program is substantial and clinically relevant.

Conclusion

These findings support progressive RT as a strategy to offset the negative behavioral functional effects of breast cancer treatment that adversely affect the lifestyle of older BCS. This program can be accomplished at gymnasiums with standard strength training equipment; thus, it would be practical to conduct larger, community-based trials to confirm these preliminary findings and assess the longer term health-related benefits of RT in more BCS. Future studies also should consider the randomization of participants to appropriate control groups and the combined effects of RT with other lifestyle interventions, including aerobic exercise and dietary modification.

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Mean $\pm$ SEM. Significant change from baseline: * $P < 0.05$; ‡ $P < 0.01$.

Figure 1.

Effects of RT on relative changes in whole-body and tissue-specific inflammation.

Table 1

Effects of RT on body composition, function, and metabolism (N=11)

	Pre	Post	Paired P-value
Weight (kg)	78 ± 3	78 ± 3	0.76
Body Mass Index (kg/m ²)	30 ± 1	30 ± 1	0.56
Total body fat (%BF)	42 ± 2	42 ± 2	0.28
Total body fat-free mass (kg)	44 ± 1	45 ± 1	0.69
Mid-thigh muscle area (cm ²)	64 ± 5	70 ± 4	0.04
Visceral Abdominal Fat area (cm ²)	110 ± 23	108 ± 24	0.73
Subcutaneous Abdominal Fat area (cm ²)	354 ± 32	361 ± 36	0.41
Systolic blood pressure (mmHg)	121 ± 5	115 ± 3	0.04
Diastolic blood pressure (mmHg)	70 ± 3	66 ± 3	0.04
Fasting glucose (mmol/L)	4.8 ± 0.2	5 ± 0.2	0.54
Fasting insulin (pmol/L)	58 ± 8	47 ± 6	0.04
HOMA-IR	2.0 ± 0.3	1.8 ± 0.2	0.35
2-hr glucose (mmol/L)	6.6 ± 0.8	6.4 ± 0.5	0.79
Triglycerides (mmol/L)	1.12 ± 0.14	1.39 ± 0.2	0.14
Total cholesterol (mmol/L)	5.7 ± 0.3	5.6 ± 0.3	0.54
HDL-cholesterol (mmol/L)	1.9 ± 0.2	1.8 ± 0.2	0.48
LDL-cholesterol (mmol/L)	3.3 ± 0.3	3.2 ± 0.2	0.80
1 RM strength chest press (lbs)	54 ± 5	68 ± 6	<0.01
1 RM strength knee extension (lbs)	62 ± 5	80 ± 7	<0.01
1 RM strength leg press (lbs)	244 ± 11	312 ± 20	<0.01
Chair stand time (s)	9.6 ± 0.8	8.1 ± 0.5	0.01
6MWD (m)	532 ± 24	555 ± 21	0.03
Gait speed (m/s)	1.32 ± 0.13	1.33 ± 0.10	0.95
VO ₂ max (ml/kg/min)	24 ± 2	25 ± 1	0.08
Accelerometry activity counts (counts/d)	130,737 ± 36,954	127,408 ± 20,807	0.65
Resting metabolic rate (kcal/d)	1,305 ± 274	1,356 ± 238	0.62
Caloric intake (kcal/d)	1,933 ± 627	1,847 ± 555	0.44

Mean±SEM. HOMA-IR: homeostatic model assessment of insulin resistance; 6MWD: six-minute walk distance.