

Effects of Aerobic and Resistance Exercise in Breast Cancer Patients Receiving Adjuvant Chemotherapy: A Multicenter Randomized Controlled Trial

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A B S T R A C T

Purpose

Breast cancer chemotherapy may cause unfavorable changes in physical functioning, body composition, psychosocial functioning, and quality of life (QOL). We evaluated the relative merits of aerobic and resistance exercise in blunting these effects.

Patients and Methods

We conducted a multicenter randomized controlled trial in Canada between 2003 and 2005 that randomly assigned 242 breast cancer patients initiating adjuvant chemotherapy to usual care (n = 82), supervised resistance exercise (n = 82), or supervised aerobic exercise (n = 78) for the duration of their chemotherapy (median, 17 weeks; 95% CI, 9 to 24 weeks). Our primary end point was cancer-specific QOL assessed by the Functional Assessment of Cancer Therapy–Anemia scale. Secondary end points were fatigue, psychosocial functioning, physical fitness, body composition, chemotherapy completion rate, and lymphedema.

Results

The follow-up assessment rate for our primary end point was 92.1%, and adherence to the supervised exercise was 70.2%. Unadjusted and adjusted mixed-model analyses indicated that aerobic exercise was superior to usual care for improving self-esteem ($P = .015$), aerobic fitness ($P = .006$), and percent body fat (adjusted $P = .076$). Resistance exercise was superior to usual care for improving self-esteem ($P = .018$), muscular strength ($P < .001$), lean body mass ($P = .015$), and chemotherapy completion rate ($P = .033$). Changes in cancer-specific QOL, fatigue, depression, and anxiety favored the exercise groups but did not reach statistical significance. Exercise did not cause lymphedema or adverse events.

Conclusion

Neither aerobic nor resistance exercise significantly improved cancer-specific QOL in breast cancer patients receiving chemotherapy, but they did improve self-esteem, physical fitness, body composition, and chemotherapy completion rate without causing lymphedema or significant adverse events.

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INTRODUCTION

Adjuvant combination chemotherapy for early-stage breast cancer improves survival, but it may also cause unfavorable changes in quality of life (QOL),¹ fatigue,² physical functioning,³ and body composition.⁴ Few interventions have been shown to prevent these declines. Although exercise training has been considered, few studies have focused on breast cancer patients receiving chemotherapy, and the quality of the evidence is modest.⁵⁻⁷ In particular, study samples have been small and/or clinically heterogeneous (ie, mixed cancer sites on mixed treatment

modalities), and no study has compared aerobic with resistance exercise. Moreover, few studies have examined body composition end points or lymphedema rates, and no study has documented chemotherapy completion rates. Consequently, the safety, efficacy, and optimal mode of exercise training in breast cancer patients receiving chemotherapy are still unknown.

Here, we report results from the Supervised Trial of Aerobic Versus Resistance Training (START), which examined the independent effects of aerobic and resistance exercise on QOL, fatigue, psychosocial functioning, physical fitness, body

composition, chemotherapy completion rates, and lymphedema rates in breast cancer patients receiving adjuvant chemotherapy. We hypothesized that both aerobic exercise training (AET) and resistance exercise training (RET) would be superior to usual care (UC) for the patient-rated outcomes. For the objective outcomes, we hypothesized that AET would have beneficial effects on aerobic fitness and body fat levels, whereas RET would have beneficial effects for muscular strength and lean body mass. We did not expect either exercise intervention to cause lymphedema or interfere with chemotherapy completion rates.

PATIENTS AND METHODS

Setting and Participants

Participants were recruited from the Cross Cancer Institute (Edmonton, Alberta, Canada), the Ottawa Hospital Integrated Cancer Program (Ottawa, Ontario, Canada), and the British Columbia Cancer Agency (Vancouver, British Columbia, Canada). The trial received ethical approval from all three centers and written informed consent from all participants. Eligibility criteria included English- or French-speaking nonpregnant women ≥ 18 years old with stage I to IIIA breast cancer who were beginning first-line adjuvant chemotherapy. Women were excluded if they had incomplete axillary surgery, transabdominal rectus abdominus muscle reconstructive surgery, uncontrolled hypertension, cardiac illness, psychiatric illness, or if they were otherwise not approved by their oncologist.

Design and Procedures

The study was a prospective, three-armed, randomized controlled trial. Eligible participants were identified by their treating oncologist before chemotherapy. Interested participants completed a questionnaire, physical fitness test, and dual x-ray absorptiometry scan (added after the first 23 participants were randomly assigned).

Random Assignment

Participants were stratified by center and chemotherapy protocol (taxane based v non-taxane based) and randomly assigned to AET, RET, or UC in a 1:1:1 ratio using a computer-generated program. The allocation sequence was generated in Edmonton and concealed from the project directors at each site who assigned participants to groups.

Exercise Training Interventions

Participants exercised for the duration of their chemotherapy, including delays, beginning 1 to 2 weeks after starting chemotherapy and ending 3 weeks after chemotherapy. Warm-up and cool-down periods were 5 minutes of light aerobic activity and stretching. The AET group was asked to exercise three times per week on a cycle ergometer, treadmill, or elliptical beginning at 60% of their maximal oxygen consumption, or VO_{2max} , for weeks 1 to 6 and progressing to 70% during weeks 7 to 12 and 80% beyond week 12.⁸ Exercise duration began at 15 minutes for weeks 1 to 3 and increased by 5 minutes every 3 weeks until the duration reached 45 minutes at week 18. The RET group were asked to exercise three times per week performing two sets of eight to 12 repetitions of nine different exercises at 60% to 70% of their estimated one-repetition maximum.⁹ The exercises were leg extension, leg curl, leg press, calf raises, chest press, seated row, triceps extension, biceps curls, and modified curl-ups. Resistance was increased by 10% when participants completed more than 12 repetitions. The UC group was asked not to initiate an exercise program and was offered a 1-month exercise program after postintervention assessments.

Assessment of Primary and Secondary End Points

Patient-rated outcomes were assessed at baseline (1 to 2 weeks after starting chemotherapy), midpoint (middle of chemotherapy), after the intervention (3 to 4 weeks after chemotherapy), and the 6-month follow-up (data not presented). Cancer-specific QOL and fatigue were assessed by the Functional Assessment of Cancer Therapy–Anemia scale.¹⁰ Psychosocial

functioning was assessed by the Rosenberg Self-Esteem Scale,¹¹ the Center for Epidemiological Studies Depression Scale,¹² and the Spielberger State Anxiety Inventory.¹³

Objectively measured outcomes were assessed at baseline and after intervention. Aerobic fitness was evaluated using a maximal incremental exercise protocol on a treadmill.¹⁴ Expired gases were analyzed using a metabolic measurement cart (CPX-D; Medical Graphics, St Paul, MN). Peak oxygen consumption was determined by taking the highest values during a 15-second period. Muscular strength was assessed by an eight-repetition maximum on the horizontal bench press and leg extension.¹⁵ The maximum weight and number of repetitions were used to estimate the one-repetition maximum.¹⁵ Body weight to the nearest 0.1 kg and standing height to the nearest 0.5 cm were assessed without shoes using a balance beam scale (Health-o-Meter; Jarden Corporation, Rye, NY). A dual x-ray absorptiometry scan was obtained for the assessment of whole body fat and lean tissue using the Hologic QDR-4500 (Hologic, Bedford, MA) in Vancouver and the General Electric LUNAR EXPERT (GE, Piscataway, NJ) in Ottawa and Edmonton. Lymphedema was assessed using standard volumetric arm measurements based on water displacement.¹⁶ Chemotherapy completion rate was assessed as the average relative dose-intensity (RDI) for the originally planned regimen based on standard formulas.^{17,18}

Assessment of Covariates, Exercise Adherence, and Adverse Events

Demographic and behavioral data were collected by self-report, and medical data were abstracted from records. Exercise trainers monitored adherence and adverse events. Nonprotocol exercise was assessed by self-report.¹⁹

Statistical Analyses and Sample Size Calculation

With 80 participants per group, our trial had 0.80 power to detect a difference in change scores of 7 points (standard deviation = 16) on the Functional Assessment of Cancer Therapy–Anemia scale¹⁰ with a loss-to-follow-up of 10%, a two-tailed $\alpha < .05$, and no adjustment for multiple testing. Baseline comparisons were performed using univariate analysis of variance for continuous variables and χ^2 analyses for categorical variables. Mixed-model analysis was used to model each outcome measure at three (or two) time points and compare the differences across groups in changes over time.²⁰ Our primary analysis was unadjusted, but we also performed adjusted analyses controlling for baseline value of the outcome, age, marital status, employment status, disease stage, chemotherapy protocol, exercise status, and smoking status, using baseline propensity scores²¹ for being assigned to the RET and AET groups. We provide descriptive data and 95% CIs for all possible comparisons but provide significance tests (*P* values) only for hypothesized comparisons. For all analyses, we used the intent-to-treat principle. Available data for participants with missing data were included under the missing at random assumption of the mixed-model analysis.

RESULTS

Recruitment was from February 2003 to July 2005 (Fig 1). We recruited 242 (33%) of 736 eligible participants. The most common reasons for refusal were lack of interest ($n = 131$), too far to travel ($n = 96$), and too busy ($n = 64$). We obtained follow-up data on the patient-rated outcomes from 223 (92.1%) of 242 participants (Fig 1), which did not differ by group ($P = .379$). The most common reason for loss to follow-up was that the participant was unreachable after multiple attempts ($n = 9$).

The groups were balanced at baseline (Table 1). The median length of the exercise intervention was 17 weeks (95% CI, 9 to 24 weeks), and the mean length of treatment was 17 ± 4 weeks. The AET and RET groups attended 72.0% (2,685 of 3,750 sessions) and 68.2% (2,810 of 4,079 sessions) of their supervised exercise sessions, respectively ($P = .411$). The AET group met their

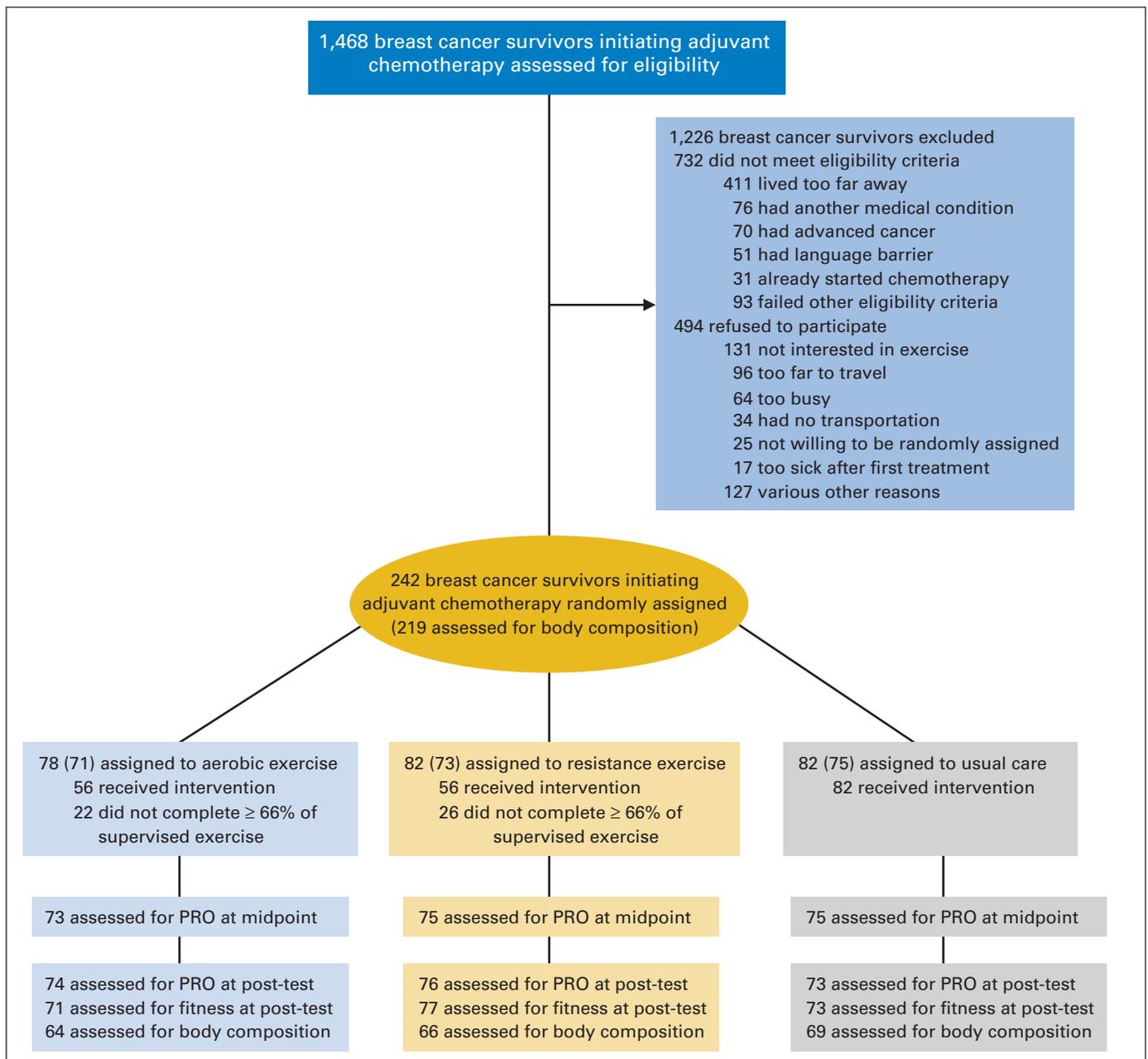


Fig 1. Flow of participants through the trial. PRO, patient-rated outcomes.

prescribed duration and intensity 95.6% and 87.2% of the time, respectively. The RET group completed all nine exercises, two sets each, and eight to 12 repetitions each set 96.8%, 96.9%, and 94.5% of the time, respectively. Less than 15% of participants reported regular exercise outside of the trial, which did not differ by group ($P > .2$).

Changes in Patient-Rated Outcomes

Table 2 presents the patient-rated outcomes. Self-esteem was superior in the AET ($P = .015$) and RET ($P = .018$) groups compared with UC. All other changes in patient-rated outcomes favored the exercise groups but did not reach statistical significance. Results were unchanged after adjustment for covariates (Table 2).

Changes in Objectively Measured Outcomes

Table 3 lists the physical fitness end points. Peak oxygen consumption was superior in the AET group compared with the UC ($P = .006$) and RET ($P = .014$) groups. Lower body and upper body strength were superior in the RET compared with the UC ($P < .001$) and AET ($P < .001$) groups. Results were unchanged after adjustment for covariates (Table 3). Table 4 lists the body composition end points. Lean body mass was superior in the RET group compared with the UC group ($P = .015$). Adjusted analyses showed that the AET group was borderline superior to the UC group in percent body fat (adjusted $P = .076$). The percentage of participants who experienced a ≥ 200 -mL increase in the difference between their affected and

Exercise During Breast Cancer Chemotherapy

Table 1. Baseline Demographic, Medical, and Behavioral Profile of Participants Overall and by Group Assignment

Variable	Overall (n = 242)		Usual Care (n = 82)		RET (n = 82)		AET (n = 78)		P
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Demographic profile									
Age, years									.946
Mean	49.2		49.0		49.5		49.0		
Range	25-78		26-78		25-76		30-75		
Married	154	63.6	51	62.2	47	57.3	56	71.8	.155
Completed university	155	64.0	53	64.6	51	62.2	51	65.4	.907
Income > \$80,000/yr*	103	45.0	34	42.5	41	53.9	28	38.4	.138
Full-time employed	72	29.8	23	28.0	29	35.4	20	25.6	.371
Medical profile									
Weight, kg									.282
Mean	70.6		72.6		69.7		69.4		
SD	14.3		15.2		14.4		13.3		
BMI, kg/m ²									.518
Mean	26.6		27.1		26.1		26.7		
SD	5.5		5.4		5.5		5.6		
Obese	50	20.7	19	23.2	14	17.1	17	21.8	.600
Hypertension	17	7.0	4	4.9	8	9.8	5	6.4	.458
Postmenopausal	89	36.8	27	32.9	35	42.7	27	34.6	.558
Disease stage									
I (T1N0)	60	24.8	20	24.4	22	26.8	18	23.1	.344
IIa (T1N1, T2N0)	99	40.9	30	36.6	36	43.9	33	42.3	
IIb (T2N1, T3N0)	48	19.8	22	26.8	9	11.0	17	21.8	
IIIa (T1N2, T2N2, T3N1-2)	35	14.5	10	12.2	15	18.3	10	12.8	
Surgical protocol									
Breast conservation	143	59.1	49	59.8	50	61.0	44	56.4	.857
Chemotherapy protocol									
Nontaxane									
FE ₁₀₀ C	74	30.6	23	28.0	29	35.4	22	28.2	.749
AC	64	26.4	20	24.4	23	28.0	21	26.9	
CE ₁₂₀ F	16	6.6	8	9.8	5	6.1	3	3.8	
Other	13	5.4	3	3.7	1	1.2	9	11.5	
Taxane									
TAC	34	14.0	10	12.2	12	14.6	12	15.4	
AC-Taxane	33	13.6	14	17.1	10	12.2	9	11.5	
Other	8	3.3	4	4.9	2	2.4	22.6		
Behavioral profile									
Current exerciser	64	26.4	27	32.9	22	26.8	15	19.2	.145
Current weight trainer	19	7.9	9	11.3	6	7.3	4	5.1	.351
Current smoker	20	8.3	5	6.1	9	11.0	6	7.7	.513
Current drinker	15	6.2	5	6.1	4	4.9	6	7.7	.761

Abbreviations: RET, resistance exercise training; AET, aerobic exercise training; SD, standard deviation; BMI, body mass index; FE₁₀₀C, fluorouracil, epirubicin, cyclophosphamide; CE₁₂₀F, cyclophosphamide, epirubicin, fluorouracil; AC, doxorubicin, cyclophosphamide; AC-Taxane, paclitaxel or docetaxel after AC; TAC, docetaxel, doxorubicin, cyclophosphamide.
*N = 229.

unaffected arm volumes from baseline to after intervention was 7.3% (six of 82 patients) in the UC group, 3.7% (three of 82 patients) in the RET group, and 9.0% (seven of 78 patients) in the AET group ($P = .381$).

Chemotherapy Completion Rate

RDI was 84.1% in the UC group compared with 89.8% in the RET group (mean difference = 5.7%; 95% CI, 0.4% to 11.0%; $P = .033$) and 87.4% in the AET group (mean difference = 3.3%; 95% CI, -2.5% to 9.2%; $P = .266$). The percentage of participants who received $\geq 85\%$ of their planned RDI was 65.9% (54 of 82 patients) in the UC group compared with 78.0% (64 of 82 patients) in the RET

group (mean difference = 12.1%; $P = .082$) and 74.4% (58 of 78 patients) in the AET group (mean difference = 8.5%; $P = .241$).

Associations Among Exercise Adherence and Changes in End Points

Exercise adherence in both groups was positively associated with a higher RDI ($r = 0.17$; $P = .035$). AET adherence was associated with greater improvements in aerobic fitness ($r = 0.24$; $P = .036$). RET adherence was associated with greater improvements in lower body strength ($r = 0.61$; $P < .001$), upper body strength ($r = 0.53$; $P < .001$), and lean body mass ($r = 0.25$; $P = .037$). For the AET versus UC comparison, improvements in aerobic fitness were associated

Table 2. Effects of Aerobic and Resistance Exercise on Patient-Rated Outcomes in Breast Cancer Patients Receiving Chemotherapy

Outcome	Baseline		Midpoint		Post-Test		Mean Change		Unadjusted Group Difference in Mean Change			Adjusted Group Difference in Mean Change		
	Mean	SD	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	<i>P</i>	Mean	95% CI	<i>P</i>
FACT-An														
UC	135.3	28.1	131.1	29.5	139.9	28.2	1.0	-4.2 to 6.3	4.7*	-2.7 to 12.1	.216	4.0*	-3.4 to 11.5	.286
RET	132.2	23.5	132.6	28.4	140.9	24.8	5.9	0.6 to 11.2	3.7†	-3.8 to 11.1	.338	3.6†	-3.9 to 11.2	.345
AET	135.7	29.0	135.5	27.2	144.7	25.2	4.8	-0.6 to 10.1	1.0‡	-6.4 to 8.5		0.4‡	-7.1 to 8.0	
Self-esteem														
UC	34.1	4.6	32.9	5.1	33.2	5.5	-1.0	-1.8 to -0.3	1.3*	0.2 to 2.3	.018	1.2*	0.2 to 2.3	.025
RET	34.1	4.2	33.8	4.8	34.7	4.2	0.3	-0.5 to 1.0	1.3†	0.3 to 2.4	.015	1.2†	0.1 to 2.3	.026
AET	34.0	5.1	34.1	5.0	34.5	5.1	0.3	-0.5 to 1.1	0.0‡	-1.1 to 1.0		0.0‡	-1.1 to 1.1	
Fatigue														
UC	34.6	11.1	32.3	12.3	34.9	12.5	-0.7	-3.2 to 1.8	1.5*	-2.0 to 5.0	.393	1.7*	-1.8 to 5.2	.338
RET	34.3	10.1	33.1	11.3	36.3	9.4	0.9	-1.6 to 3.3	1.0†	-2.5 to 4.5	.561	1.5†	-2.1 to 5.0	.415
AET	35.3	12.1	34.0	11.5	36.8	10.4	0.4	-2.1 to 2.9	0.5‡	-3.0 to 4.0		0.2‡	-3.3 to 3.8	
Anxiety														
UC	42.0	13.7	39.0	11.9	37.4	12.0	-4.2	-6.5 to -1.9	-1.5*	1.8 to -4.8	.372	-1.8*	1.5 to -5.1	.278
RET	42.0	12.0	37.0	12.0	36.4	12.7	-5.7	-8.0 to -3.4	-1.7†	1.6 to -5.0	.317	-2.1†	1.2 to -5.5	.209
AET	40.9	13.3	35.3	11.9	35.0	11.7	-5.9	-8.3 to -3.5	0.2‡	3.5 to -3.1		0.3‡	3.1 to -3.7	
Depression														
UC	13.9	9.7	13.7	10.2	10.8	9.4	-1.9	-3.8 to 0.1	-0.4*	2.4 to -3.2	.774	-0.6*	2.2 to -3.4	.679
RET	13.8	10.1	12.6	9.4	10.6	9.5	-2.3	-4.3 to -0.3	-0.3†	2.5 to -3.1	.841	-0.8†	2.0 to -3.6	.571
AET	12.8	9.8	12.2	9.8	9.7	9.3	-2.2	-4.2 to -0.2	-0.1‡	2.7 to -2.9		0.2‡	3.1 to -2.6	

NOTE. Mean (SD) at midpoint and post-test are based on available data. Mean change is based on combined post-test/midpoint scores minus baseline score but may not precisely reflect this difference given that mean change is estimated based on mixed-model analysis. Adjusted group difference in mean change was adjusted for baseline value of the outcome, age, marital status, employment status, disease stage, chemotherapy protocol, current exercise status, and smoking status. *P* values presented only for hypothesized comparisons.

Abbreviations: SD, standard deviation; FACT-An, Functional Assessment of Cancer Therapy–Anemia; UC, usual care; RET, resistance exercise training; AET, aerobic exercise training.

*RET v UC.

†AET v UC.

‡RET v AET.

with improvements in QOL ($r = 0.26$; $P = .001$), fatigue ($r = 0.25$; $P = .002$), depression ($r = -0.24$; $P = .003$), and anxiety ($r = -0.18$; $P = .025$). For the RET versus UC comparison, improvements in lean body mass were associated with improvements in QOL ($r = 0.19$; $P = .022$), self-esteem ($r = 0.19$; $P = .022$), depression ($r = -0.19$; $P = .019$), and percentage of participants completing $\geq 85\%$ of their planned RDI ($r = 0.15$; $P = .074$). Improvement in lower body strength was associated with improvement in QOL ($r = 0.15$; $P = .057$).

Adverse Events

Two participants experienced an adverse event related to exercise after baseline maximal treadmill testing. One participant became lightheaded, hypotensive, and moderately nauseous. A second participant experienced dizziness, weakness, and mild diarrhea. Both participants recovered quickly.

DISCUSSION

Contrary to our hypotheses, neither AET nor RET significantly improved cancer-specific QOL, fatigue, depression, or anxiety, although the trends favored the exercise groups. Consistent with our hypotheses, AET significantly improved self-esteem, preserved aerobic fitness, and maintained body fat levels, whereas RET significantly improved self-esteem, muscular strength, and lean body mass. Unexpectedly,

RET significantly improved chemotherapy completion rate. Neither intervention caused lymphedema or significant adverse events.

Few published studies are available for direct comparisons. A recent meta-analysis⁵ of 14 exercise randomized controlled trials in breast cancer patients/survivors revealed that published trials have either focused on the postadjuvant therapy setting or combined breast cancer patients on various adjuvant therapies (eg, chemotherapy, radiation therapy, hormonal therapy). Trials in the postadjuvant setting have shown that both aerobic²² and resistance²³ exercise can improve cancer-specific QOL. Only one trial in the adjuvant therapy setting reported data separately for patients on chemotherapy, although it was not powered for such a subanalysis.²⁴ In that trial, there were no effects of 26 weeks of lower intensity supervised or self-directed aerobic exercise on QOL.

The failure of our exercise interventions to significantly improve cancer-specific QOL may be, in part, a result of the wide variability in QOL change scores we found during chemotherapy (standard deviation = 25). Many uncontrollable factors influence QOL during chemotherapy, and a global measure of cancer-specific QOL may be too broad to detect the likely narrower effects of exercise training. A more appropriate and realistic primary end point in exercise trials may be the physical functioning component of QOL.²⁵ It is also possible that the effects of our exercise interventions were partly diluted by inadequate adherence and/or an insufficient volume/intensity of exercise. However, it is unclear whether better adherence or a greater volume/

Table 3. Effects of Aerobic and Resistance Exercise on Physical Fitness in Breast Cancer Patients Receiving Chemotherapy

Measure	Baseline		Post-Test		Mean Change		Unadjusted Group Differences in Mean Change			Adjusted Group Differences in Mean Change		
	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	P	Mean	95% CI	P
VO_{2peak}, mL/kg/min												
UC	24.8	6.2	23.5	5.4	-1.6	-2.6 to -0.7	1.8*	0.5 to 3.2	.006	2.0*	0.6 to 3.3	.004
RET	25.5	6.1	24.2	6.1	-1.4	-2.4 to -0.5	1.6†	0.3 to 2.9	.014	1.4†	0.1 to 2.7	.031
AET	25.2	7.2	25.7	7.4	0.2	-0.7 to 1.1	0.2‡	-1.1 to 1.5		0.5‡	-0.8 to 1.8	
VO_{2peak}, L/min												
UC	1.76	0.40	1.68	0.36	-0.10	-0.16 to -0.03	0.13*	0.04 to 0.22	.004	0.12*	0.03 to 0.21	.010
RET	1.73	0.35	1.67	0.36	-0.06	-0.12 to -0.00	0.09†	0.01 to 0.18	.035	0.08†	-0.01 to 0.17	.077
AET	1.72	0.43	1.77	0.48	0.03	-0.03 to 0.09	0.03‡	-0.05 to 0.12		0.04‡	-0.05 to 0.12	
1RM leg, kg												
UC	25.6	12.6	27.1	14.1	1.4	-0.5 to 3.3	6.7‡	4.0 to 9.3	.001	6.8‡	4.2 to 9.5	.001
RET	24.4	11.2	32.8	12.6	8.2	6.4 to 10.1	4.9§	2.3 to 7.6	.001	5.2§	2.5 to 7.9	.001
AET	24.8	12.5	28.2	14.2	3.3	1.3 to 5.2	1.7*	-1.0 to 4.4		1.6*	-1.1 to 4.3	
1RM chest, kg												
UC	22.8	8.9	24.6	7.8	1.5	-0.4 to 3.4	7.4‡	5.2 to 9.6	.001	7.7‡	5.5 to 9.9	.001
RET	23.2	7.2	31.9	10.8	8.8	7.2 to 10.3	6.1§	3.9 to 8.4	.001	6.8§	4.5 to 9.0	.001
AET	22.1	7.5	24.7	7.5	2.6	1.0 to 4.3	1.3*	-1.0 to 3.6		1.0*	-1.3 to 3.2	

NOTE. Mean (SD) at post-test is based on available data. Mean change is based on post-test score minus baseline score but may not precisely reflect this difference given that mean change is estimated based on mixed-model analysis. Adjusted group difference in mean change was adjusted for baseline value of the outcome, age, marital status, employment status, disease stage, chemotherapy protocol, current exercise status, and smoking status. P values presented only for hypothesized comparisons.

Abbreviations: SD, standard deviation; VO_{2peak}, peak volume of oxygen consumed; UC, usual care; RET, resistance exercise training; AET, aerobic exercise training; RM, repetition maximum.

*AET v UC.

†AET v RET.

‡RET v UC.

§RET v AET.

intensity of exercise can be achieved in this clinical setting. Our adherence rate is within the range commonly reported in exercise RCTs in breast cancer patients receiving adjuvant therapy⁵ and older adults without cancer.²⁶ Nevertheless, there is clearly still room for improvement, and we plan a full report of the predictors of exercise adherence in our trial to facilitate this improvement.

Changes in fatigue, depression, and anxiety also favored the exercise groups but did not achieve statistical significance. These findings are consistent with three recent meta-analyses⁵⁻⁷ that have reported modest effects on these outcomes and noted that the stronger and more consistent effects appear in the postadjuvant setting. Conversely, both exercise interventions improved self-esteem, which is an important outcome for breast cancer patients going through difficult treatments.²⁷ There is no identified important difference for our scale, but the standardized effect size was small to moderate (*d* = 0.30). Previous exercise trials have not examined self-esteem during chemotherapy but have noted improvements in the postadjuvant therapy setting with aerobic exercise.²²

Although patient-rated outcomes primarily showed trends in favor of the exercise groups, the objectively measured outcomes were reliably changed. AET blunted a decline in maximal oxygen consumption in the UC group of approximately 2.0 mL/mg/kg, or 8%. Training studies in other populations show slightly larger improvements of 10% to 30%,⁸ although few have conducted intent-to-treat analyses. Segal et al²⁴ reported no effects of a lower intensity exercise program on aerobic fitness in the subanalysis of breast cancer patients receiving chemotherapy. Our trial demonstrates that a higher intensity exercise program can preserve aerobic fitness in breast cancer patients even in

the face of a downward trajectory in aerobic fitness, possibly caused by chemotherapy effects such as anemia, tachycardia, dehydration, and cardiac dysfunction.^{3,28} Preserving aerobic fitness in breast cancer patients receiving chemotherapy may be beneficial. In our trial, improved aerobic fitness was associated with improved QOL, fatigue, depression, and anxiety, suggesting that greater increases in aerobic fitness may have resulted in better patient-rated outcomes. Aerobic fitness is also an established predictor of disease and mortality.²⁹

RET increased muscular strength by 25% to 35%, which is consistent with research in other populations.⁹ To our knowledge, our study is the first to test the effects of an isolated resistance training program in breast cancer patients receiving chemotherapy. Schmitz et al³⁰ demonstrated improvements in muscular strength of 30% to 50% in the postadjuvant setting. The clinical implications of improved muscular strength for breast cancer patients are unknown, but we did observe a modest correlation between increased muscular strength and improved QOL, as did Ohira et al.²³ In other populations, muscular strength is associated with improved physical functioning, reduced mobility limitations and lower risk of falling,^{23,31,32} and lower mortality.³³

Neither exercise intervention prevented weight gain, but each altered body composition as hypothesized. AET prevented fat gain, and RET added lean body mass. Weight gain after a breast cancer diagnosis has been associated with earlier recurrence and shorter survival,³⁴ with most explanations focusing on adiposity rather than body weight per se.³⁵ Moreover, in our trial, improvements in body composition were associated with improvements in QOL, self-esteem, and depression, suggesting that body composition may have implications

Table 4. Effects of Aerobic and Resistance Exercise on Body Weight and Composition in Breast Cancer Patients Receiving Chemotherapy

Measure	Baseline		Post-Test		Mean Change		Unadjusted Group Differences in Mean Change			Adjusted Group Differences in Mean Change		
	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	P	Mean	95% CI	P
Body weight, kg												
UC	72.6	15.2	73.4	15.7	1.2	0.4 to 2.0	-0.2*	0.9 to -1.3	.737	-0.2*	0.9 to -1.4	.698
RET	69.7	14.4	71.1	15.4	1.6	0.8 to 2.4	0.4†	1.6 to -0.7		0.5†	1.6 to -0.6	
AET	69.4	13.3	70.3	13.8	1.0	0.2 to 1.8	-0.6‡	0.5 to -1.8		-0.7‡	0.4 to -1.9	
Body fat, %												
UC	38.8	9.1	39.8	8.8	1.0	0.3 to 1.7	-0.8*	0.2 to -1.8	.137	-0.9*	0.1 to -1.9	.076
RET	37.2	9.0	37.2	9.0	0.3	-0.4 to 1.1	-0.6†	0.4 to -1.6		-0.9†	0.1 to -1.9	
AET	37.8	8.9	37.9	8.9	0.2	-0.5 to 0.9	-0.2‡	0.9 to -1.2		-0.0†	1.0 to -1.0	
Fat mass, kg												
UC	28.3	12.0	29.5	12.0	1.0	0.4 to 1.7	-0.5*	0.4 to -1.5	.261	-0.7*	0.3 to -1.6	.170
RET	26.2	11.7	26.9	12.0	0.9	0.3 to 1.6	-0.1†	0.8 to -1.1		-0.2	0.8 to -1.2	
AET	26.6	11.5	27.1	11.3	0.5	-0.2 to 1.2	-0.4‡	0.5 to -1.4		-0.5‡	0.5 to -1.5	
Lean mass, kg												
UC	40.8	5.3	40.9	5.6	0.2	-0.3 to 0.6	0.8†	0.2 to 1.5	.015	1.0†	0.3 to 1.6	.004
RET	40.3	4.6	41.3	4.9	1.0	0.5 to 1.5	0.4*	-0.3 to 1.0		0.3*	-0.3 to 1.0	
AET	40.3	4.8	40.9	5.1	0.5	0.1 to 1.0	0.4§	-0.2 to 1.1		0.6§	-0.1 to 1.3	
Arm difference, mL												
UC	21	134	11	153	-4	-35 to 26	0.0†	-43 to 42		-5†	-46 to 35	
RET	8	129	10	118	-5	-35 to 25	14*	-29 to 57		-9*	-50 to 32	
AET	-18	101	-7	152	10	-21 to 40	-14§	-57 to 28		-4§	-45 to 38	

NOTE. Mean (SD) at post-test is based on available data. Mean change is based on post-test score minus baseline score but may not precisely reflect this difference given that mean change is estimated based on mixed-model analysis. Adjusted group difference in mean change was adjusted for baseline value of the outcome, age, marital status, employment status, disease stage, chemotherapy protocol, current exercise status, and smoking status. *P* values presented only for hypothesized comparisons.

Abbreviations: SD, standard deviation; UC, usual care; RET, resistance exercise training; AET, aerobic exercise training.

*AET v UC.

†RET v UC.

‡AET v RET.

§RET v AET.

for psychosocial functioning in addition to clinical outcomes. Schmitz et al³⁰ reported similar improvements in body composition with resistance training in the postadjuvant setting but also found no change in body weight. Associations between improved lean body mass and QOL were also reported.²³ A systematic review of 14 exercise intervention studies in breast cancer patients/survivors concluded that there were few changes in body weight but some improvements in body composition.³⁶

Unexpectedly, RET improved chemotherapy completion rate. Clinical trials support the importance of sustaining full dose-intensity in adjuvant chemotherapy for early-stage breast cancer with evidence of a threshold effect of approximately 85%.³⁷⁻³⁹ The clinical implications of an RDI difference of 5.7% found in our study are unclear, but most studies have noted a steep association between RDI and clinical outcomes to the 85% threshold.³⁷⁻³⁹ The explanation for the difference in chemotherapy completion rate is unclear. The groups were balanced on chemotherapy regimens, and the UC group actually received more granulocyte colony-stimulating factor than the RET group (*P* = .013) after excluding prophylactic granulocyte colony-stimulating factor use. Acute exercise is known to cause demargination of neutrophils and a temporary increase of 25% to 100% in peripheral-blood neutrophil count lasting up to 6 hours,⁴⁰ which, theoretically, could alter chemotherapy delivery decisions. Given the exploratory nature of this finding, it should be replicated before it is considered reliable.

Neither AET nor RET caused arm swelling or other adverse events. To our knowledge, our trial is the first to report lymphedema data for the adjuvant chemotherapy time period, but it is consistent with previous smaller studies in the postadjuvant therapy setting.^{16,41-43} Few exercise trials in breast cancer patients have reported adverse events, but our trial suggests that adverse events may be minimal.

Our trial's strengths include the direct comparison of aerobic and resistance exercise, the largest sample size to date, the well-defined population, the multicenter recruitment, the supervised exercise, a comprehensive assessment of important end points with validated measures, intent-to-treat analysis, and limited loss to follow-up. Limitations include the 70% adherence rate, the 33% recruitment rate, and the well-educated, racially homogenous sample. Moreover, given the 22 group comparisons we made at the $\alpha = .05$ level, we would expect one false discovery by chance if all of these comparisons were actually null.

In summary, our trial demonstrates important improvements in self-esteem, physical fitness, body composition, and possibly chemotherapy completion rate from exercise training in breast cancer patients receiving chemotherapy. Our findings may help explain a recent observational study reporting a positive association between physical activity and survival in breast cancer survivors.⁴⁴ Cancer care professionals should consider recommending either AET or RET to breast cancer patients receiving chemotherapy. A combined intervention

may be optimal, but research is needed to confirm this assumption, especially given the challenges of exercise adherence in this clinical setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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