Randomized Controlled Trial of Exercise Training in Postmenopausal Breast Cancer Survivors: Cardiopulmonary and Quality of Life Outcomes

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Purpose: **To determine the effects of exercise training on cardiopulmonary function and quality of life (QOL) in postmenopausal breast cancer survivors who had completed surgery, radiotherapy, and/or chemotherapy with or without current hormone therapy use.**

Methods: **Fifty-three postmenopausal breast cancer survivors were randomly assigned to an exercise (n = 25) or control (n = 28) group. The exercise group trained on cycle ergometers three times per week for 15 weeks at a power output that elicited the ventilatory equivalent for carbon dioxide. The control group did not train. The primary outcomes were changes in peak oxygen consumption and overall QOL from baseline to postintervention. Peak oxygen consumption was assessed by a graded exercise test using gas exchange analysis. Overall QOL was assessed by the Functional Assessment of Cancer Therapy–Breast scale.**

Results: **Fifty-two participants completed the trial. The exercise group completed 98.4% of the exercise sessions. Baseline values for peak oxygen consumption ($P = .254$) and overall QOL ($P = .286$) did not differ between groups. Peak oxygen consumption increased by 0.24 L/min in the exercise group, whereas it decreased by 0.05 L/min in the control group (mean difference, 0.29 L/min; 95% confidence interval [CI], 0.18 to 0.40; $P < .001$). Overall QOL increased by 9.1 points in the exercise group compared with 0.3 points in the control group (mean difference, 8.8 points; 95% CI, 3.6 to 14.0; $P = .001$). Pearson correlations indicated that change in peak oxygen consumption correlated with change in overall QOL ($r = 0.45$; $P < .01$).**

Conclusion: **Exercise training had beneficial effects on cardiopulmonary function and QOL in postmenopausal breast cancer survivors.**

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BREAST CANCER is a prevalent disease[1] that requires intense and prolonged treatments.[2] Cardiopulmonary capacity may be compromised in breast cancer survivors because of the pathology of the disease, therapeutic regimens, and weight gain and inactivity secondary to treatment. The reduction in cardiopulmonary capacity may lead to reductions in quality of life (QOL)[3,4] or premature death.[5-7]

Research has provided preliminary evidence for the safety, feasibility, and efficacy of exercise training in breast cancer survivors.[8,9] Few studies, however, have been randomized controlled trials.[8] Overall, little is known about the impact of exercise training on cardiopulmonary function and QOL in breast cancer survivors. The role of exercise training in recovery after treatments may be particularly important because not all breast cancer survivors seem willing or able to tolerate exercise during adjuvant therapies.[10] However, QOL may be still be compromised in the months and years after treatment.[11]

The Rehabilitation Exercise for Health After Breast Cancer (REHAB) trial was a randomized controlled trial designed to determine the effects of supervised exercise training on cardiopulmonary, QOL, and biologic outcomes in postmenopausal breast cancer survivors who had completed surgery, radiotherapy, and/or chemotherapy with or without current hormone therapy use. Here we report the effects of exercise training on the cardiopulmonary and QOL outcomes. The primary outcomes were changes in peak oxygen consumption and overall QOL between baseline and postintervention. We hypothesized that exercise training would have beneficial effects on both of these outcomes. We also hypothesized that the changes in cardiopulmonary function would be correlated with the changes in QOL. Effects on the biologic outcomes will be reported separately.

METHODS

Setting and Participants

The trial was conducted at the Cross Cancer Institute (CCI) and University of Alberta (Edmonton, Alberta, Canada). The Alberta Cancer Board and the University of Alberta approved the trial. Written informed consent was obtained for all procedures.

Eligibility criteria included histologically confirmed early-stage breast cancer with no evidence of recurrent or progressive disease; diagnosis between January 1999 and June 2000; completed surgery, radiotherapy, and/or chemotherapy with or without current hormone therapy use; postmenopausal status (not experiencing menstrual periods for previous 12

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months); nonsmoking status (not smoking for previous 12 months); age between 50 and 69 years; English-speaking; and willingness to travel to the exercise facility. Eligible participants were not admitted if they had known cardiac disease, uncontrolled hypertension, thyroid disease, diabetes, mental illness, infection, immune or endocrine abnormality, or contraindications to exercise on the basis of an exercise stress test.

Experiment Design and Recruitment

The study was a prospective, randomized controlled trial. A random sample of female breast cancer survivors was obtained from the Alberta Cancer Registry and the referring physician was contacted for approval. A recruitment letter was mailed to each approved survivor who then contacted the project director by telephone if interested. Eligible and interested survivors were mailed a package that contained a cover letter, two copies of an informed consent form, and a questionnaire. A cardiopulmonary exercise test and blood collection were scheduled at that time.

Random Assignment to Treatment

Participants were stratified by type of adjuvant therapy (previous chemotherapy versus no previous chemotherapy, and current hormone therapy versus no current hormone therapy) and randomly assigned to the exercise or control group using a random-numbers table.[12] A block permutation procedure was used to generate the allocation sequence within each strata. The allocation sequence and group assignments were generated by a research assistant and then enclosed in sequentially numbered and sealed envelopes. The contents of the envelopes were concealed from the project director, who assigned participants to groups.

Blinding

Exercise physiologists with no knowledge of the participant's group assignment performed the cardiopulmonary exercise tests and determined scores at baseline and postintervention. Participants were blinded to their exercise test results until after the trial.

Exercise Training Intervention

Exercise training was supervised and based on each participant's cardiopulmonary fitness level at baseline. Missed sessions were rescheduled. Participants trained three times per week for 15 weeks on recumbent or upright cycle ergometers (Lifestyle Fitness 9500HR; Life Fitness, Franklin Park, IL). Exercise intensity was set at the power output that elicited the ventilatory equivalent for carbon dioxide to ensure optimal training adaptations.[13,14] This training intensity corresponds to approximately 70% to 75% of maximal oxygen consumption in untrained subjects.[15,16] Exercise duration began at 15 minutes for weeks 1 through 3, and then systematically increased by 5 minutes every 3 weeks thereafter to 35 minutes for weeks 13 through 15. Warm-up and cool-down periods consisted of 5 minutes of cycling at the power output of the ventilatory equivalent for oxygen (approximately 50% of peak oxygen consumption). The control group did not train. To reduce attrition, control group participants were offered the intervention after the trial.

Outcomes

The primary outcomes were changes in peak oxygen consumption and overall QOL between baseline and postintervention. Secondary cardiopulmonary outcomes were changes in peak power output, oxygen consumption and power output at the ventilatory equivalent for oxygen, and oxygen consumption and power output at the ventilatory equivalent for carbon dioxide. Secondary QOL outcomes were changes in happiness, self-esteem, fatigue, and various subscales of overall QOL. Secondary body composition outcomes were changes in body weight, body mass index, and sum of skinfolds.

Cardiopulmonary Outcomes

Cardiopulmonary outcomes were evaluated using an incremental exercise protocol on a Monark cycle ergometer (Varberg, Sweden). Participants cycled at 60 rpm with no workload for 3 minutes to adapt to the cycle ergometer. Participants then performed continuous and incremental 2-minute workloads at 60 rpm until the criteria for peak oxygen consumption was reached. The initial power output was 30 W and each subsequent power output increased by 15 W. Participants were encouraged throughout the test. Criteria for peak oxygen consumption included any two of the following: a peak or plateau in oxygen consumption concurrent with increased power output; a respiratory exchange ratio ≥ 1.0; volitional exhaustion; and a rating of perceived exertion greater than 19. Heart rate and blood pressure assessments were obtained at the end of each workload. Exercise was terminated if participants developed severe dyspnea, dizziness, or chest pain, or had an abnormal blood pressure or heart rate response.

Expired gases were collected and analyzed every 15 seconds using a metabolic measurement cart (SensorMedics Horizon Metabolic Cart, Anaheim, CA). The metabolic system was calibrated for volume at the start of each day and for gas concentrations before and after every test. Peak oxygen consumption, the ventilatory equivalent for oxygen, and the ventilatory equivalent for carbon dioxide were determined by taking the mean of four consecutive 15-second values at the end of the respective power output. The ventilatory equivalents for oxygen and carbon dioxide were determined using the method described previously.[16] Participants were asked to follow the same diet (including approximately the same macronutrient content) for 3 days before both baseline and postprogram exercise testing.

QOL Outcomes

Overall QOL was assessed by the Functional Assessment of Cancer Therapy–Breast (FACT-B) scale.[17] The FACT-B contains subscales for physical (seven items), functional (seven items), emotional (six items), and social or family (six items; this scale normally has seven items, but we did not include the "satisfaction with sex life" item because of previous significant missing data) well-being that comprise the FACT–General (FACT-G) scale, plus a breast cancer subscale (nine items). The five subscales were summed to obtain the FACT-B score (all 35 items). We also computed the FACT-G score (26 items, excluding the breast cancer subscale) and a trial outcome index (TOI) score (23 items consisting of physical and functional well-being plus the breast cancer subscale).[17]

Happiness was assessed by the Happiness Measure (HM).[18] The HM contains a question asking for the amount of time spent happy, unhappy, and neutral in the past week.[18] We used percentage of time spent happy in the past week. Self-esteem was assessed by the Rosenberg Self-Esteem Scale,[19] which has been a widely used measure of self-esteem in the psychosocial oncology literature.[20] Fatigue was assessed by the 13-item Fatigue Scale (FS) of the FACT measurement system developed specifically for the cancer population.[21]

Body Composition Outcomes

Body composition was assessed indirectly through changes in body weight, body mass index, and subcutaneous sum of skinfolds. Body weight was assessed using an electronic scale (model 2100; Tanita, Arlington Heights, IL). Standing height was determined without shoes. Body mass index was calculated as weight in kilograms divided by height in meters squared. Subcutaneous sum of skinfolds was assessed using John Bull calipers (British Indicators Ltd, London, United Kingdom) at five standard sites (biceps, triceps, subscapular, suprailiac, and medial calf).[22]

Adherence to the Exercise Intervention

The exercise trainers monitored adherence to the intervention. To monitor exercise outside of the exercise intervention, we used the Leisure Score Index of the Godin Leisure-Time Exercise Questionnaire.[23,24] Participants completed the Leisure Score Index every two weeks over the 15-week intervention.

Baseline Characteristics

Demographic data were collected by self-report. Medical data were abstracted from medical records.

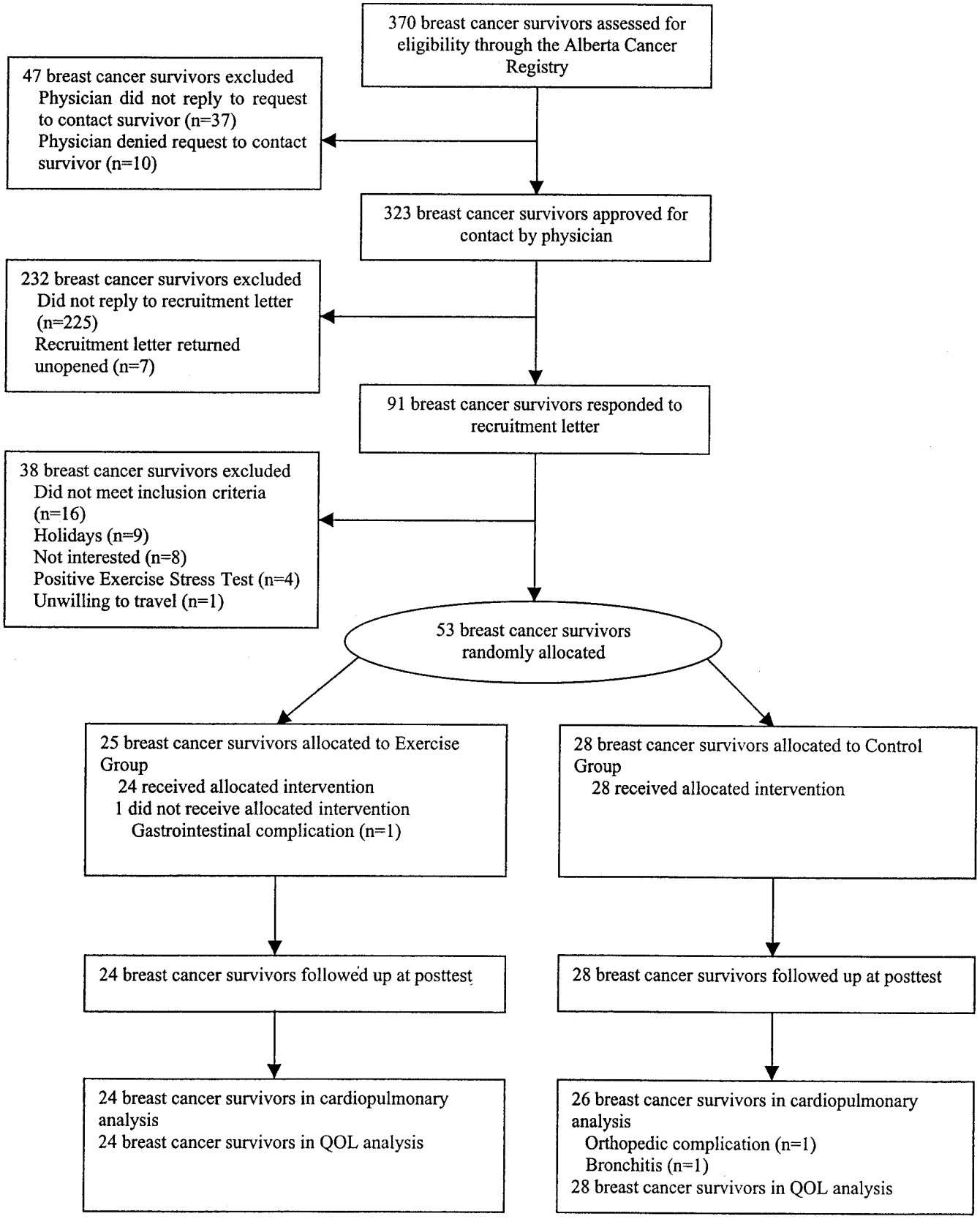

Fig 1. Flow of participants through the trial. QOL, quality of life.

Table 1. Baseline Characteristics*

Characteristic	Overall (n = 52)	Exercise Group (n = 24)	Control Group (n = 28)	P†
Demographic				
Age, years	59 (6)	59 (5)	58 (6)	.712
Married	39 (75%)	18 (75%)	21 (75%)	.99
Completed university	23 (44%)	7 (29%)	16 (56%)	.058
Family income > $60,000/year	23 (44%)	10 (44%)	13 (48%)	.741
Employed full time	15 (29%)	7 (29%)	8 (29%)	.962
Medical				
Weight, kg	78.7 (18.1)	78.1 (20.4)	79.4 (16.4)	.801
Body mass index, kg/m^2	29.2 (6.6)	29.4 (7.4)	29.1 (6.1)	.880
Sum of skinfolds, mm	134.3 (40.5)	136.8 (45.1)	132.1 (36.5)	.682
Months postsurgery, RT, and/or CT	14 (6)	14 (6)	14 (7)	.856
Stage				
I (T1N0)	21 (40%)	10 (42%)	11 (39%)	.862
IIa (T1N1, T2N0)	17 (33%)	6 (25%)	11 (39%)	.274
IIb (T2N1, T3N0)	11 (21%)	6 (25%)	5 (18%)	.530
IIIa (T1N2, T2N2, T3N1–2)	3 (6%)	2 (8%)	1 (4%)	.463
Surgery				
Mastectomy	28 (54%)	15 (64%)	13 (46%)	.246
Lumpectomy	24 (46%)	9 (37%)	15 (54%)	.246
Radiation Therapy	37 (71%)	16 (67%)	21 (75%)	.508
Chemotherapy	21 (40%)	10 (42%)	11 (39%)	.862
Anthracycline regimen	20 (38%)	10 (42%)	10 (36%)	.329
Current hormone therapy use	24 (46%)	11 (46%)	13 (46%)	.966
Surgery alone	8 (15%)	4 (17%)	6 (14%)	
Surgery plus RT	12 (23%)	6 (25%)	6 (21%)	
Surgery plus RT and CT	8 (15%)	3 (13%)	5 (18%)	
Surgery plus RT, CT, and HT	10 (19%)	5 (21%)	5 (18%)	
Surgery plus HT	4 (8%)	2 (8%)	2 (7%)	
Surgery plus RT and HT	7 (14%)	2 (8%)	5 (18%)	
Surgery plus CT and HT	3 (6%)	2 (8%)	1 (4%)	.935
Past exercise				
Moderate, minutes	82 (114)	62 (94)	98 (126)	.247
Strenuous, minutes	25 (61)	23 (56)	26 (65)	.897
Moderate to strenuous, minutes	106 (129)	85 (102)	124 (146)	.280
>90 Moderate to strenuous, minutes	22 (42%)	10 (42%)	12 (42.9%)	.931

Abbreviations: RT, radiation therapy; CT, chemotherapy; HT, hormone therapy.

*Data are presented as the mean (SD) for continuous variables and frequency (percentage) for categorical variables.

†*P* value for difference between groups.

Sample Size Calculation and Statistical Analyses

We needed 25 participants in each group to detect a large standardized effect ($d = 0.80$) in our primary outcomes with a power of 0.80 and a two-tailed alpha less than 0.05. Effect size d is computed by dividing the difference in means between groups by the SD and is interpreted as $d = 0.20$ (small), $d = 0.50$ (medium), and $d = 0.80$ (large).[25] To compensate for nonassessable participants, 53 participants were enrolled. Our prespecified intention-to-treat analysis was defined as participants who were randomly assigned to treatment and for whom follow-up data were available.

Data were analyzed using SPSS Version 10.0 software (SPSS Inc, Chicago, IL). We compared baseline characteristics and adverse events of the two groups using independent-samples t tests for continuous data and Pearson's χ^2 tests for categorical data. Our primary analysis used independent-samples t tests to compare changes between groups in outcomes from baseline to postintervention. Data were also analyzed using analysis of covariance procedures in which groups were compared according to the postintervention value with the baseline value as the covariate.

Pearson's product moment correlations were used to evaluate the association between changes in cardiopulmonary function and changes in QOL. Multiple regression analyses were used to provide a statistical test of the possible mediating role of cardiopulmonary function.[26] The multiple regression approach requires that the outcome of interest (ie, QOL) be regressed on the proposed mediator (ie, cardiopulmonary function) and the intervention (ie, the experimental group dummy coded as 0 = control and 1 = exercise). Mediation is suspected in cases where the proposed mediator maintains a significant relationship with the outcome, whereas the effect of the intervention is no longer significant (on the basis of standardized regression coefficients). Such a case suggests that the proposed mediator statistically accounts for the effect of the intervention on the outcome. For the mediation analyses, we selected two possible mediators (changes in peak oxygen consumption and peak power output) and six key QOL outcomes (changes in the FACT-B, happiness, self-esteem, fatigue, FACT-G, and TOI).

RESULTS

Flow of Participants Through the Trial

Participant recruitment took place in May and June 2001. Baseline assessments were completed in July 2001 and follow-up assessments were conducted in November 2001. Figure 1 shows the flow of participants through the trial.

Baseline Characteristics

Table 1 presents the baseline characteristics. The groups were balanced in terms of demographic, medical, and past exercise variables.

Table 2. Effects of Exercise Training on Cardiopulmonary Outcomes*

Variable	Baseline			Postintervention		Change		Difference Between Groups		
	Mean	SD	P†	Mean	SD	Mean	SD	Mean Change	95% CI	P‡
Primary outcome										
Peak oxygen consumption, L/min										
Exercise group	1.38	0.30		1.61	0.29	+0.24	0.24			
Control group	1.48	0.32	.254	1.43	0.31	−0.05	0.14	+.29	0.18 to 0.40	< .001
Secondary outcomes										
Peak oxygen consumption, mL/kg/min										
Exercise group	18.6	3.9		21.3	3.7	+2.7	2.6			
Control group	18.8	3.8	.807	18.2	3.9	−0.6	1.7	+3.4	2.1 to 4.6	< .001
Peak power output, W										
Exercise group	99.4	21.6		113.6	23.6	+14.2	18.7			
Control group	108.8	21.9	.137	92.3	21.3	−16.5	18.6	+30.7	20.1 to 41.3	< .001
Peak respiratory exchange ratio										
Exercise group	1.13	0.09		1.13	0.07	−0.002	0.06			
Control group	1.13	0.06	.928	1.14	0.07	+0.005	0.06	−0.007	−0.042 to 0.027	.663
Peak heart rate, beats/min										
Exercise group	155	20		157	16	+2	11			
Control group	160	17	.393	156	16	−4	7	+6	1 to 11	.025
Ventilatory equivalent for oxygen, L/min										
Exercise group	0.86	0.16		1.04	0.27	+0.18	0.31			
Control group	0.89	0.16	.474	0.93	0.17	+0.03	0.14	+0.15	0.02 to 0.28	.030
Power output at the ventilatory equivalent for oxygen, W										
Exercise group	49.5	12.5		59.5	13.7	+10.0	14.4			
Control group	57.2	10.8	.023	47.9	13.3	−9.3	10.5	+19.3	12.2 to 26.5	< .001
Ventilatory equivalent for carbon dioxide, L/min										
Exercise group	1.03	0.21		1.34	0.28	+0.31	0.28			
Control group	1.05	0.20	.720	1.12	0.18	+0.07	0.14	+0.24	0.11 to 0.36	< .001
Power output at the ventilatory equivalent for carbon dioxide, W										
Exercise group	65.7	14.5		84.0	19.8	+18.3	18.1			
Control group	73.5	11.9	.042	66.6	14.8	−6.9	11.8	+25.2	16.6 to 33.8	< .001

Abbreviation: CI, confidence interval.

*Exercise group (n = 24); control group (n = 26).

†*P* value for difference between groups at baseline.

‡*P* value for change between groups from baseline to postintervention.

Adverse Events

Five participants (20.8%) in the exercise group experienced an adverse event compared with two participants (7.1%) in the control group ($P = .168$). The adverse events in the exercise group were lymphedema (n = 3), gynecologic complication (n = 1), and influenza (n = 1). The control group's events were foot fracture (n = 1) and bronchitis (n = 1). There was a trend toward a higher incidence of lymphedema in the exercise group ($P = .054$).

Adherence to the Exercise Training Intervention

The exercise group completed 98.4% (44.3 of 45) of the prescribed exercise sessions. Non–protocol-related exercise was less than 15 minutes of moderate to strenuous exercise per week and was not different between groups ($P = .890$).

Changes in Cardiopulmonary Function

Table 2 lists the cardiopulmonary outcomes. The baseline value for peak oxygen consumption did not differ between groups ($P = .254$). Peak oxygen consumption increased by 0.24 L/min in the exercise group, whereas it decreased by 0.05 L/min in the control group ($P < .001$). Differences between groups in changes from baseline to postintervention were also observed for peak power output ($P < .001$), oxygen consumption at the ventilatory equivalent for oxygen ($P = .030$) and carbon dioxide ($P < .001$), and power output at the ventilatory equivalent for oxygen ($P < .001$) and carbon dioxide ($P < .001$).

Changes in QOL

Table 3 lists the QOL outcomes. The baseline value for overall QOL did not differ between groups ($P = .286$). Overall QOL increased by 9.1 points in the exercise group compared with 0.3 points in the control group ($P = .001$). Differences between groups in changes from baseline to postintervention were also observed for happiness ($P = .019$), self-esteem ($P = .010$), fatigue ($P = .006$), the FACT-B subcomponents of FACT-G ($P = .016$), TOI ($P = .001$), physical well-being ($P = .001$), and the breast cancer subscale ($P = .001$).

Changes in Body Composition

Table 4 lists the body composition outcomes. Baseline values for body weight ($P = .801$), body mass index ($P = .881$), and

Table 3. Effect of Exercise Training on Quality of Life Outcomes*

Variable (scale range)	Baseline			Postintervention		Change		Difference Between Groups		
	Mean	SD	P†	Mean	SD	Mean	SD	Mean Change	95% CI	P‡
Primary outcome										
FACT-B (0-140)										
Exercise group	110.5	19.0		119.6	16.9	+9.1	14.1			
Control group	115.5	12.4	.286	115.8	14.9	+0.3	8.5	+8.8	3.6 to 14.0	< .001
Secondary outcomes										
Happiness, % time happy										
Exercise group	48.1	27.1		65.4	24.6	+17.3	26.1			
Control group	57.5	21.3	.168	58.3	22.4	+0.8	23.0	+16.5	2.8 to 30.2	.019
Self-esteem (10-40)										
Exercise group	32.2	5.6		34.8	4.7	+2.6	3.7			
Control group	34.7	4.5	.068	34.6	4.4	−0.1	3.5	+2.7	0.7 to 4.7	.010
Fatigue, 0-52										
Exercise group	17.6	11.5		8.3	7.9	−9.3	10.2			
Control group	10.8	8.8	.024	8.8	8.1	−2.0	7.5	−7.3	−12.2 to −2.3	.006
Components of FACT-B										
FACT-G, 0-104										
Exercise group	85.5	12.4	.291	91.3	11.0	+5.7	7.4			
Control group	88.8	9.0		89.3	10.9	+0.6	7.4	+5.2	1.0 to 9.3	.016
TOI, 0-92										
Exercise group	70.8	13.7	.209	77.0	12.0	+6.2	7.2			
Control group	74.9	9.4		74.8	10.1	−0.1	8.5	+6.3	2.8 to 9.7	< .001
Physical well-being (0-28)										
Exercise group	23.3	3.6	.019	25.3	2.5	+1.9	2.0	+2.1	0.9 to 3.3	< .001
Control group	25.4	2.6		25.3	2.8	−0.2	2.2			
Functional well-being (0-28)										
Exercise group	22.5	4.3		23.4	4.0	+0.9	2.8			
Control group	22.8	3.8	.763	23.1	4.0	+0.4	2.7	+0.6	−1.0 to 2.1	.468
Emotional well-being (0-24)										
Exercise group	19.2	3.9		21.5	3.4	+2.3	3.1			
Control group	19.4	2.8	.965	20.3	3.0	+0.8	2.9	+1.4	−0.2 to 3.1	.090
Social/family well-being (0-24)										
Exercise group	20.5	3.7		21.1	3.5	+0.6	2.4			
Control group	21.1	3.3	.304	20.7	3.6	−0.5	3.3	+1.1	−0.5 to 2.8	.180
Breast cancer subscale (0-36)										
Exercise group	25.0	7.6		28.4	6.7	+3.3	4.0			
Control group	26.7	4.6	.528	26.4	5.1	−0.3	3.2	+3.6	1.6 to 5.6	< .001

Abbreviations: CI, confidence interval; FACT-B, Functional Assessment of Cancer Therapy–Breast; FACT-G, Functional Assessment of Cancer Therapy–General; TOI, trial outcome index.

*Exercise group (n = 24); control group (n = 28).

†*P* value for difference between groups at baseline.

‡*P* value for change between groups from baseline to postintervention.

sum of skinfolds ($P = .596$) did not differ between groups. There were no differences between groups for changes in body weight or body mass index, but there was a trend toward a change in sum of skinfolds. Sum of skinfolds decreased by 4.9 mm in the exercise group, whereas it increased by 5.1 mm in the control group ($P = .095$).

Analyses of Covariance

Analyses of covariance indicated that the observed changes in all cardiopulmonary, QOL, and body composition outcomes were independent of the baseline values, except for fatigue, which approached significance ($P = .100$).

Associations Between Cardiopulmonary Function and QOL

Table 5 lists the zero-order correlations between changes in cardiopulmonary function and changes in QOL. Change in peak oxygen consumption correlated with change in overall QOL ($r = 0.45$; $P < .01$). Other significant correlations were observed.

Table 6 summarizes the multiple regression analyses. For change in peak oxygen consumption as the mediator, we found evidence of statistical mediation for changes in overall QOL (peak oxygen consumption beta = 0.30, $P = .066$; experimental group beta = 0.24, $P = .149$) and the TOI (peak oxygen consumption beta = 0.32, $P = .049$; experimental group beta = 0.25, $P = .116$), but not self-esteem (peak oxygen consumption beta = −0.01, $P = .959$; experimental group beta = 0.42, $P = .016$). For change in peak power output as the mediator, we found evidence of statistical mediation for change in fatigue (peak power output beta = −0.49, $P = .004$; experimental group beta = −0.07, $P = .645$) and the TOI (peak power output beta = 0.37, $P = .027$; experimental group beta = 0.21, $P = .195$), but not self-esteem (peak

Table 4. Effect of Exercise Training on Body Composition Outcomes*

Variable	Baseline			Postintervention		Change		Difference Between Groups		
	Mean	SD	P†	Mean	SD	Mean	SD	Mean Change	95% CL	P‡
Body Weight, kg										
Exercise group	78.1	20.4		78.2	20.5	+0.1	2.0			
Control group	79.4	16.4	.801	80.1	16.2	+0.7	1.8	+0.6	−0.6, 1.6	.332
Body mass index, kg/m^2										
Exercise group	29.4	7.4		29.4	7.4	+0.0	0.7			
Control group	29.1	6.1	.881	29.3	6.0	+0.3	0.7	+0.3	−0.3, 0.6	.325
Sum of skinfolds, mm										
Exercise group	136.8	45.1		131.9	46.4	−4.9	15.7			
Control group	132.1	36.5	.596	137.1	44.4	+5.1	24.4	+10.2	−1.8, 21.6	.095

Abbreviation: CL, confidence limit.

*Exercise group (n = 24); control group (n = 26).

†*P* value for difference between groups at baseline.

‡*P* value for change between groups from baseline to postintervention.

power output beta = 0.06, $P = .735$; experimental group beta = 0.38, $P = .036$). Results for the other QOL outcomes were inconclusive.

DISCUSSION

In support of our hypotheses, we found that exercise training had beneficial effects on changes in peak oxygen consumption and overall QOL. We also found evidence for beneficial effects on changes in peak power output, submaximal cardiopulmonary function, happiness, self-esteem, fatigue, and several subcomponents of overall QOL. Moreover, changes in cardiopulmonary function were associated with changes in QOL and there was some evidence of statistical mediation.

The strengths and limitations of our trial merit comment. Strengths include the randomized controlled trial design, validated measures of peak oxygen consumption and QOL, a high exercise adherence rate, and minimal loss to follow-up. Limitations include a 14% recruitment rate that may restrict the generalizability of our findings, a small sample size, and a short exercise intervention with no long-term follow-up.

Table 5. Correlations Between Changes in Cardiopulmonary Capacity and Changes in Quality of Life (n = 50)

Changes in Quality of Life	Changes in Cardiopulmonary Capacity	
	Peak Oxygen Consumption	Peak Power Output
FACT-B	0.45†	0.42†
Happiness	0.29*	0.35*
Self-esteem	0.25	0.30*
Fatigue	−0.41†	−0.54†
FACT-G	0.37†	0.31*
TOI	0.47†	0.50†
Physical well-being	0.29*	0.38†
Functional well-being	0.35*	0.28*
Emotional well-being	0.27	0.28
Social or family well-being	0.17	0.00
Breast cancer subscale	0.42†	0.47†

Abbreviations: FACT-B, Functional Assessment of Cancer Therapy–Breast; FACT-G, Functional Assessment of Cancer Therapy–General; TOI, trial outcome index.

*$P < .05$.

†$P < .01$ (two-tailed).

One main finding of our trial was that exercise training had a beneficial effect on peak oxygen consumption. Peak oxygen consumption increased by 17.4% in the exercise group, whereas it decreased by 3.4% in the control group. The magnitude of this treatment effect is comparable to that observed in randomized trials of exercise training in chronic heart failure and heart transplantation patients, which have shown effects between 15% and 31%.[27-29] The implication of this change for breast cancer survival is unknown. Nevertheless, a recent prospective study of 6,213 men reported that the magnitude of change in exercise capacity that we observed in the present trial was associated with a 12% improvement in survival.[7]

The mechanism by which exercise training increased peak oxygen consumption in breast cancer survivors remains to be determined. Research in older postmenopausal women has shown that adaptations to skeletal muscles are involved in exercise training–induced improvements in peak oxygen consumption.[30,31] Skeletal muscle changes include increases in oxidative enzymes, capillary density, myoglobin concentrations, muscle glycogen, and adaptation of muscle fiber to a higher percentage of type I fibers.[32] Improved peak oxygen consumption after exercise training is also associated with an increased cardiac output and greater arteriovenous oxygen content difference.[33] It is therefore reasonable to assume that both mechanisms contributed to the physiologic adaptations observed in this trial.[33]

A second main finding of our trial was that exercise training had a beneficial effect on overall QOL. We found a change of almost 9 points in the FACT-B and more than 5 points in the FACT-G. A change of 4 or more points in the FACT-G is considered a minimal clinically important difference (CID),[34] but no such guideline is available for the FACT-B. It seems likely, however, that a minimal CID for the FACT-B would not exceed 9 points because it comprises the FACT-G plus only the breast cancer subscale. Moreover, the change in overall QOL is approximately a medium standardized effect size ($d = 0.50$), which is approximately twice that reported in a meta-analysis of other cognitive-behavioral interventions for cancer survivors.[35] Additional analyses of the subscales indicated beneficial effects for the TOI, physical well-being, and breast cancer subscale.

Table 6. Multiple Regression of Changes in Quality of Life on Changes in Peak Cardiopulmonary Function and Experimental Group (n = 50)

	Standardized Regression Coefficients (beta)				Standardized Regression Coefficients (beta)			
	Peak Oxygen Consumption Change		Experimental Group		Peak Power Output Change		Experimental Group	
Variable	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*
FACT-B change	0.30	.066	0.24	.149	0.26	.131	0.26	.136
Happiness change	0.18	.302	0.17	.338	0.28	.117	0.10	.583
Self-esteem change	−0.01	.959	0.42	.016	0.06	.735	0.38	.036
Fatigue change	−0.28	.102	−0.22	.187	−0.49	.004	−0.07	.645
FACT-G change	0.27	.119	0.16	.338	0.17	.337	0.22	.230
TOI change	0.32	.049	0.25	.116	0.37	.027	0.21	.195

Abbreviations: FACT-B, Functional Assessment of Cancer Therapy–Breast; FACT-G, Functional Assessment of Cancer Therapy–General; TOI, trial outcome index.

These subscales contain items that mainly reflect physical and functional well-being, which are still relevant in the months after treatment.[11]

We also found that exercise training had a beneficial effect on happiness. The percentage of time spent happy in the exercise group increased by an absolute amount of 17.3% compared with 0.8% in the control group. If we assume a 16-hour waking day, this percentage improvement translates into an additional 19 hours of happiness per week, or about one additional day of happiness per week. This effect is arguably the most clinically important because it represents an indicator of overall psychological well-being. No previous study in cancer survivors has examined the effects of exercise training on happiness but future studies are clearly warranted.

Our intervention also produced a change in fatigue of more than 7 points. The magnitude of this change is more than double the 3-point guideline for a minimal CID in this scale.[34] This finding should be interpreted with caution, however, because the analysis of covariance results indicated that some of this change may have been the result of a difference at baseline. Nevertheless, fatigue is a common and distressing symptom of the cancer experience[36-38] that can still be present in long-term breast cancer survivors.[39] Few interventions have been shown to effectively treat fatigue,[40] and rest is often recommended by physicians.[38] Our finding is consistent with a growing body of research showing that exercise training can help manage fatigue in cancer survivors.[41-44] Consequently, exercise training may merit recognition as a primary treatment for fatigue in cancer survivors.

The magnitude of changes in cardiopulmonary function and QOL in our trial are considerably larger than those reported in a recent exercise trial involving breast cancer survivors during adjuvant therapy.[9] It is not clear, however, if this disparity in outcomes is the result of differences in the methods of the two trials (eg, type of exercise prescribed, intensity of the exercise, adherence rates, measure of aerobic fitness) or whether breast cancer survivors may in fact respond better to an exercise program after their treatments are over. A clinical trial that directly evaluates the optimal timing of an exercise intervention for breast cancer survivors is warranted.

Several biopsychosocial mechanisms may explain the QOL improvements in cancer survivors that result from exercise training, including cardiopulmonary adaptations, endorphins, distraction, mastery achievements, positive feedback, and social interaction. Few studies, however, have examined mechanisms of change.[45] We found that changes in cardiopulmonary function correlated with changes in QOL. Moreover, statistical tests of mediation showed that changes in overall QOL, fatigue, and the TOI may be explained by a change in peak cardiopulmonary function. It is possible, of course, that changes in QOL outcomes could also be responsible for improvements in cardiopulmonary function. The self-esteem changes were independent of aerobic fitness changes and may have resulted from increased social interaction or a sense of accomplishment in completing the exercise program.

Overall rates of adverse events were similar between the groups but the rate of lymphedema was higher in the exercise group. Two of three participants who developed lymphedema had locoregional radiotherapy that included axillary irradiation, which is a strong risk factor for lymphedema.[46,47] The relationship with the exercise intervention therefore remains unclear but future exercise trials should monitor lymphedema rates closely.

In summary, our data suggest that exercise training had beneficial effects on cardiopulmonary function and QOL in postmenopausal breast cancer survivors who had completed surgery, radiotherapy, and/or chemotherapy with or without current hormone therapy use. Improvements in cardiopulmonary function were associated with improvements in QOL. If replicated, our findings suggest that exercise training sufficient to induce cardiopulmonary adaptations should be recommended to breast cancer survivors soon after the completion of therapy.

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