VOLUME 25 · NUMBER 28 · OCTOBER 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Robert D. Reid, Christine M. Friedenreich, Aliya B. Ladha, Caroline Proulx, Jeffrey K.H. Vallance, Kirstin Lane, Yutaka Yasui, and Donald C. McKenzie

From the University of Alberta; Cross Cancer Institute, Edmonton; Alberta Cancer Board, Calgary, Alberta; Ottawa Hospital Regional Cancer Center; University of Ottawa Heart Institute, Ottawa, Ontario; British Columbia Cancer Agency; and the University of British Columbia, Vancouver, British Columbia, Canada.

Submitted July 7, 2006; accepted March 8, 2007; published online ahead of print at www.jco.org on September 4, 2007.

Supported by a grant from the Canadian Breast Cancer Research Alliance; the Canada Research Chairs Program (K.S.C. and Y.Y.); a Research Team Grant from the National Cancer Institute of Canada (NCIC) with funds from the Canadian Cancer Society (CCS) and the NCIC/CCS Sociobehavioral Cancer Research Network (K.S.C., R.J.S., D.C.M., J.R.M., C.M.F.); a New Investigator Award from the Heart and Stroke Foundation of Canada (R.D.R.); a New Investigator Award from the Canadian Institutes of Health Research and a Health Scholar Award from the Alberta Heritage Foundation for Medical Research (C.M.F.); and by a Canada Graduate Scholarship from the Canadian Institutes of Health Research and an Incentive Award from the Alberta Heritage Foundation for Medical Research (J.K.V.).

The Canadian Breast Cancer Research Alliance had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Kerry S. Courneya, PhD, Faculty of Physical Education and Recreation, University of Alberta, E-488 Van Vliet Center, Edmonton, Alberta, Canada T6G 2H9; e-mail: kerry.courneya@ualberta.ca.

0732-183X/07/2528-4396/$20.00

DOI: 10.1200/JCO.2006.08.2024

ABSTRACT

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.

J Clin Oncol 25:4396-4404. © 2007 by American Society of Clinical Oncology

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 $\geq$ 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 scale[10] 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 categoric 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 scores[21] 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 $\pm$ 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

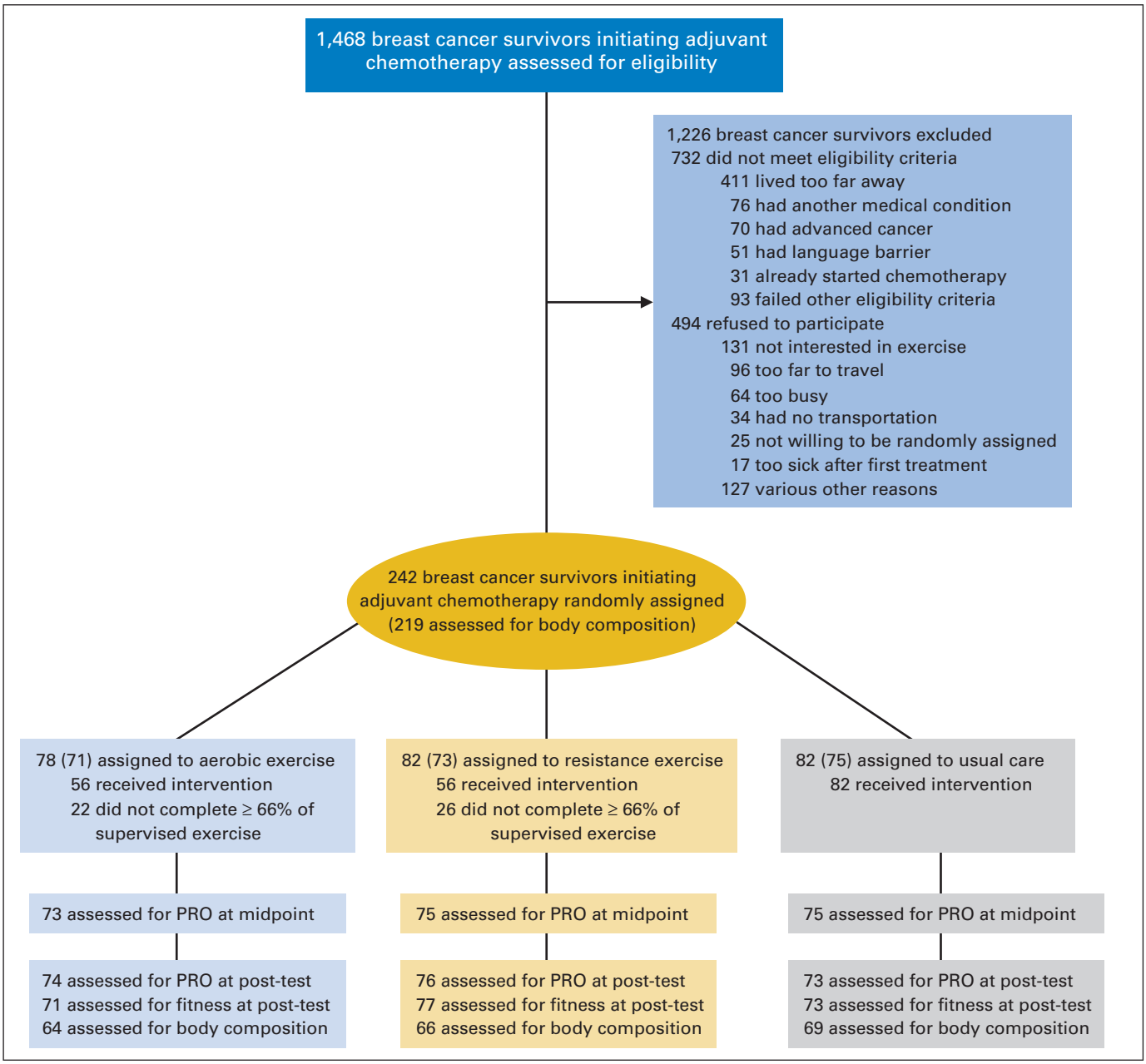

Fig 1. Flow of participants through the trial. PRO, patient-rated outcomes.

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

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									.344
I (T1N0)	60	24.8	20	24.4	22	26.8	18	23.1	
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									.857
Breast conservation	143	59.1	49	59.8	50	61.0	44	56.4	
Chemotherapy protocol									.749
Nontaxane	167	69.0	54	65.9	58	70.7	55	70.5	
$FE_{100}C$	74	30.6	23	28.0	29	35.4	22	28.2	
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	75	31.0	28	34.1	24	29.3	23	29.5	
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; $FE_{100}C$, fluorouracil, epirubicin, cyclophosphamide; $CE_{120}F$, 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 ≥ 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

	Baseline		Midpoint		Post-Test		Mean Change		Unadjusted Group Difference in Mean Change			Adjusted Group Difference in Mean Change		
Outcome	Mean	SD	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	*P*	Mean	95% CI	*P*
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 ≥ 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-analysis[5] 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 aerobic[22] and resistance[23] 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 therapy[5] 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-analyses[5-7] 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 al[24] 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 al[30] 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 al[30] 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.

AUTHOR CONTRIBUTIONS

Conception and design: Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Robert D. Reid, Christine M. Friedenreich, Aliya B. Ladha, Caroline Proulx, Jeffrey K.H. Vallance, Kirstin Lane, Donald C. McKenzie
Financial support: Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Robert D. Reid, Christine M. Friedenreich, Donald C. McKenzie
Administrative support: Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Aliya B. Ladha, Caroline Proulx, Jeffrey K.H. Vallance, Yutaka Yasui, Donald C. McKenzie
Provision of study materials or patients: Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Donald C. McKenzie
Collection and assembly of data: Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Aliya B. Ladha, Caroline Proulx, Jeffrey K.H. Vallance, Kirstin Lane, Donald C. McKenzie
Data analysis and interpretation: Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Robert D. Reid, Christine M. Friedenreich, Aliya B. Ladha, Caroline Proulx, Jeffrey K.H. Vallance, Kirstin Lane, Yutaka Yasui, Donald C. McKenzie
Manuscript writing: Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Robert D. Reid, Christine M. Friedenreich, Aliya B. Ladha, Caroline Proulx, Jeffrey K.H. Vallance, Kirstin Lane, Yutaka Yasui, Donald C. McKenzie
Final approval of manuscript: Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Robert D. Reid, Christine M. Friedenreich, Aliya B. Ladha, Caroline Proulx, Jeffrey K.H. Vallance, Kirstin Lane, Yutaka Yasui, Donald C. McKenzie

REFERENCES

1. Kayl AE, Meyers CA: Side-effects of chemotherapy and quality of life in ovarian and breast cancer patients. Curr Opin Obstet Gynecol 18:24-28, 2006
2. Kurt G, Breitbart W, Cella D, et al: Impact of cancer-related fatigue on the lives of patients: New findings from the Fatigue Coalition. Oncologist 5:353-360, 2000
3. Perez EA, Suman VJ, Davidson NE, et al: Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial. J Clin Oncol 22: 3700-3704, 2004
4. Freedman RJ, Aziz N, Albanes D, et al: Weight and body composition changes during and after adjuvant chemotherapy in women with breast cancer. J Clin Endocrinol Metab 89:2248-2253, 2004
5. McNeely M, Campbell K, Rowe B, et al: A systematic review and meta-analysis of exercise interventions in breast cancer patients and survivors. CMAJ 175:34-41, 2006
6. Conn V, Hafdahl A, Porock D, et al: A meta-analysis of exercise interventions among people treated for cancer. Support Care Cancer 14:699-712, 2006
7. Schmitz KH, Holtzman J, Courneya KS, et al: Controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 14:1588-1595, 2005
8. American College of Sports Medicine Position Stand: The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. Med Sci Sports Exerc 30:975-991, 1998
9. Kraemer WJ, Adams K, Cafarelli E, et al: American College of Sports Medicine position stand: Progression models in resistance training for healthy adults. Med Sci Sports Exerc 34:364-380, 2002
10. Cella D, Eton DT, Lai JS, et al: Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage 24:547-561, 2002
11. Rosenberg M: Society and the Adolescent Self-Image. Princeton, NJ, Princeton University Press, 1965
12. Radloff L: The use of the center for epidemiologic studies depression scale in adolescents and young adults. J Youth Adolesc 20:149-166, 1991
13. Spielberger C, Gorusch R, Lushene R: Manual for the State-Trait Anxiety Inventory. Palo Alto, CA, Consulting Psychologists Press, 1970
14. Wasserman K, Hansen J, Sue D, et al: Measurements during integrative cardiopulmonary exercise testing, in Principles of Exercise Testing and Interpretation. Baltimore, MD, Lippincott Williams & Williams, 1999
15. Landers J: Maximums based on reps. Natl Strength Cond Assoc J 6:60-61, 1985
16. Lane K, Jespersen D, McKenzie DC: The effect of a whole body exercise programme and dragon boat training on arm volume and arm circumference in women treated for breast cancer. Eur J Cancer Care 14:353-358, 2005
17. Hryniuk WM, Figueredo A, Goodyear M: Applications of dose intensity to problems in chemotherapy of breast and colorectal cancer. Semin Oncol 14:3-11, 1987 (suppl 4)
18. Longo DL, Duffey PL, DeVita VT, et al: The calculation of actual or received dose intensity: A comparison of published methods. J Clin Oncol 9:2042-2051, 1991
19. Godin G, Shephard RJ: A simple method to assess exercise behavior in the community. Can J Appl Sport Sci 10:141-146, 1985
20. Diggle P, Heagerty P, Liang K, et al: Analysis of Longitudinal Data (ed 2). New York, NY, Oxford University Press, 2002
21. Rosenbaum P, Rubin D: The central role of the propensity score in observational studies for causal effects. Biometrika 70:41-55, 1983
22. Courneya KS, Mackey JR, Bell GJ, et al: Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: Cardiopulmonary and quality of life outcomes. J Clin Oncol 21:1660-1668, 2003
23. Ohira T, Schmitz KH, Ahmed RL, et al: Effects of weight training on quality of life in recent breast cancer survivors: The Weight Training for Breast Cancer Survivors (WTBS) study. Cancer 106:2076-2083, 2006
24. Segal R, Evans W, Johnson D, et al: Structured exercise improves physical functioning in women with stages I and II breast cancer: Results of a randomized controlled trial. J Clin Oncol 19:657-665, 2001
25. Bennett JA, Winters-Stone K, Nail L: Conceptualizing and measuring physical functioning in cancer survivorship studies Oncol Nurs Forum 33:41-49, 2006
26. Martin K, Sinden A: Who will stay and who will go? A review of older adults' adherence to randomized controlled trials of exercise. J Aging Physical Activity 9:91-114, 2001
27. Fobair P, Stewart SL, Chang S, et al: Body image and sexual problems in young women with breast cancer. Psychooncology 15:579-594, 2006
28. Jensen BV, Skovsgaard T, Nielsen SL: Functional monitoring of anthracycline cardiotoxicity: A prospective, blinded, long-term observational study of outcome in 120 patients. Ann Oncol 13:699-709, 2002
29. Myers J, Prakash M, Froelicher V, et al: Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 346:793-801, 2002
30. Schmitz KH, Ahmed RL, Hannan PJ, et al: Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. Cancer Epidemiol Biomarkers Prev 14:1672-1680, 2005
31. Barnett A, Smith B, Lord SR, et al: Community-based group exercise improves balance and reduces falls in at-risk older people: A randomised controlled trial. Age Ageing 32:407-414, 2003
32. Visser M, Goodpaster BH, Kritchevsky SB, et al: Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci 60:324-333, 2005
33. Metter EJ, Talbot LA, Schrager M, et al: Skeletal muscle strength as a predictor of all-cause mortality in healthy men. J Gerontol A Biol Sci Med Sci 57:B359-B365, 2002
34. Chlebowski RT, Aiello E, McTiernan A: Weight loss in breast cancer patient management. J Clin Oncol 20:1128-1143, 2002
35. Irwin ML, McTiernan A, Baumgartner RN, et al: Changes in body fat and weight after a breast cancer diagnosis: Influence of demographic, prognostic, and lifestyle factors. J Clin Oncol 23:774-782, 2005
36. Ingram C, Courneya KS, Kingston D: Effects of exercise on body weight and composition in breast cancer survivors: An integrative systematic review. Oncol Nurs Forum 33:937-947, 2006
37. Bonadonna G, Valagussa P, Moliterni A, et al: Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. N Engl J Med 332:901-906, 1995

38. Budman DR, Berry DA, Cirrincione CT, et al: Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer: The Cancer and Leukemia Group B. J Natl Cancer Inst 90:1205-1211, 1998

39. Wood WC, Budman DR, Korzun AH, et al: Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 330:1253-1259, 1994

40. Pyne DB, Smith JA, Baker MS, et al: Neutrophil oxidative activity is differentially affected by exercise intensity and type. J Sci Med Sport 3:44-54, 2000

41. Harris SR, Niesen-Vertommen SL: Challenging the myth of exercise-induced lymphedema following breast cancer: A series of case reports. J Surg Oncol 74:95-98, 2000

42. McKenzie DC, Kalda AL: Effect of upper extremity exercise on secondary lymphedema in breast cancer patients: A pilot study. J Clin Oncol 21:463-466, 2003

43. Ahmed RL, Thomas W, Yee D, et al: Randomized controlled trial of weight training and lymphedema in breast cancer survivors. J Clin Oncol 24: 2765-2772, 2006

44. Holmes MD, Chen WY, Feskanich D, et al: Physical activity and survival after breast cancer diagnosis. JAMA 293:2479-2486, 2005

Acknowledgment

We gratefully acknowledge Lisa Workman, MA, Neil Eves, PhD, John McGavock, PhD, Kristin Campbell, PhD, Margaret McNeely, BScPT, MSc, Diana Jespersen, BA, Chris Scott, BSc, Ben Wilson, BSc, Christopher Sellar, MS, and Diane Cook, BA, for their assistance in recruitment, exercise supervision, testing, data management, and manuscript preparation.