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ARTICLE

Effects of Exercise Dose and Type During Breast Cancer Chemotherapy: Multicenter Randomized Trial

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Background Exercise improves physical functioning and symptom management during breast cancer chemotherapy, but the effects of different doses and types of exercise are unknown.

Methods A multicenter trial in Canada randomized 301 breast cancer patients to thrice-weekly supervised exercise during chemotherapy consisting of either a standard dose of 25 to 30 minutes of aerobic exercise (STAN; n = 96), a higher dose of 50 to 60 minutes of aerobic exercise (HIGH; n = 101), or a combined dose of 50 to 60 minutes of aerobic and resistance exercise (COMB; n = 104). The primary endpoint was physical functioning assessed by the Medical Outcomes Survey-Short Form (SF)–36. Secondary endpoints were other physical functioning scales, symptoms, fitness, and chemotherapy completion. All statistical tests were linear mixed model analyses, and the *P* values were two-sided.

Results Follow-up assessment of patient-reported outcomes was 99.0%. Adjusted linear mixed-model analyses showed that neither HIGH (+0.8; 95% confidence interval [CI] = –0.8 to 2.4; *P* = .30) nor COMB (+0.5; 95% CI = –1.1 to 2.1; *P* = .52] were superior to STAN for the primary outcome. In secondary analyses not adjusted for multiple comparisons, HIGH was superior to STAN for the SF-36 physical component summary (*P* = .04), SF-36 bodily pain (*P* = .02), and endocrine symptoms (*P* = .02). COMB was superior to STAN for endocrine symptoms (*P* = .009) and superior to STAN (*P* < .001) and HIGH (*P* < .001) for muscular strength. HIGH was superior to COMB for the SF-36 bodily pain (*P* = .04) and aerobic fitness (*P* = .03). No differences emerged for body composition or chemotherapy completion.

Conclusions A higher volume of aerobic or combined exercise is achievable and safe during breast cancer chemotherapy and may manage declines in physical functioning and worsening symptoms better than standard volumes.

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Aerobic and resistance exercise, either separately or in combination, have been shown to improve physical functioning and manage some symptoms in breast cancer patients receiving chemotherapy (1). Few exercise trials, however, have compared different doses or types of exercise in breast cancer patients to identify the optimal exercise prescription for a given outcome (1,2). In clinical settings outside of cancer, resistance exercise has been shown to be an important adjunct to aerobic exercise; however, few trials have controlled for the total dose of exercise, making it unclear if such a finding is a true exercise type effect (adding resistance exercise to aerobic exercise is better than adding more aerobic exercise) or simply an exercise dose effect (doing more exercise is better regardless of type) (3).

We designed the Combined Aerobic and Resistance Exercise (CARE) Trial to compare two different doses and types of exercise for improving physical functioning and symptom management in breast cancer patients receiving chemotherapy (http://clinicaltrials.gov, NCT00249015). The CARE trial addressed the dose vs type question by comparing a standard dose of 25 to 30 minutes of aerobic exercise (STAN) to a higher dose of 50 to 60 minutes of aerobic exercise (HIGH) and a combined dose of 50 to 60 minutes of aerobic and resistance exercise (COMB). We hypothesized that HIGH and COMB (a dose effect) would be superior to STAN for the patient-reported outcomes of physical functioning and symptom management. The comparison of HIGH to COMB for the patient-reported outcomes (a type effect) was considered exploratory. We did not expect either higher-dose exercise intervention to interfere with chemotherapy completion.

Methods

Setting and Participants

Participants were recruited from the Cross Cancer Institute in Edmonton, Alberta (coordinating center), Canada; the Ottawa Hospital Cancer Center in Ottawa, Ontario, Canada; and

the British Columbia Cancer Agency in Vancouver, British Columbia, Canada. The trial received ethics approval from all three centers, and written informed consent was obtained from all participants. Patients were eligible for the study if they were English- or French-speaking nonpregnant women aged 18 years or older with stage I to IIIc breast cancer initiating adjuvant chemotherapy. Women were excluded if they had incomplete axillary surgery, transabdominal rectus abdominus muscle reconstructive surgery, uncontrolled hypertension, cardiac illness, or psychiatric illness, or if they otherwise were not approved by their oncologist.

Randomization and Masking

Eligible participants were identified by their treating oncologist before chemotherapy. After baseline assessments, participants were stratified by center and chemotherapy protocol (any herceptin vs no herceptin/any taxane vs no herceptin/no taxane) and randomly assigned to STAN, COMB, or HIGH in a 1:1:1 ratio using a computer-generated program. The allocation sequence was generated in Edmonton, Canada, and concealed from the project directors at each site who assigned participants to groups. Participants and interventionists were not masked to group assignment. Outcome assessors were not masked to group assignment

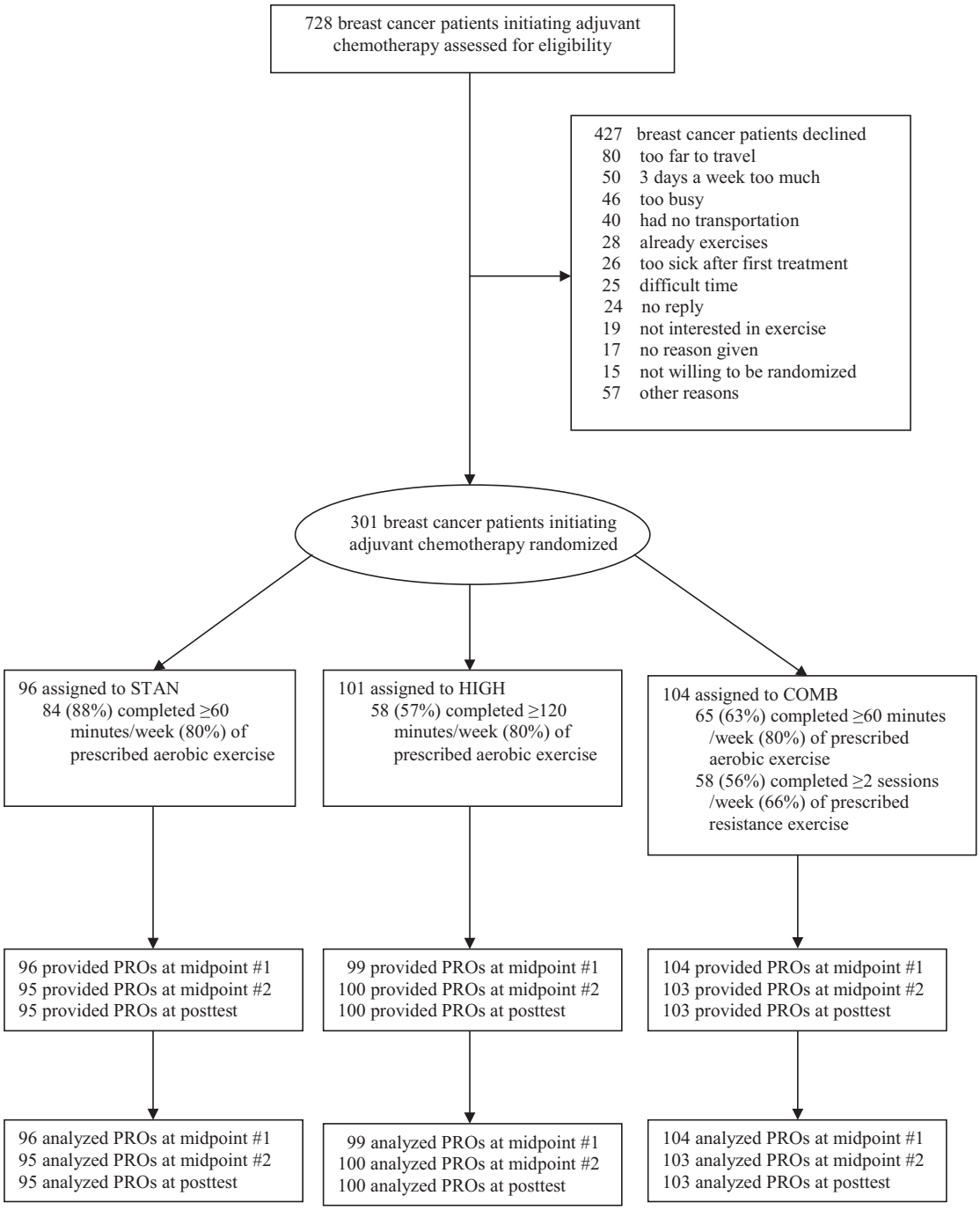

Figure 1. Flow of participants through the trial. COMB = combined aerobic and resistance exercise program; HIGH = high-volume aerobic exercise program; PRO = patient-reported outcome; STAN = standard aerobic exercise program.

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for the patient-reported outcomes or fitness assessments but were masked for the dual x-ray absorptiometry scans and chemotherapy completion evaluations.

Exercise Training Interventions

Participants exercised for the duration of their chemotherapy beginning within 1 to 2 weeks of starting chemotherapy and ending 3–4 weeks after chemotherapy. STAN followed the Physical Activity Guidelines for Americans (4), which have been endorsed for cancer survivors by the American College of Sports Medicine (1) and the American Cancer Society (5). These guidelines recommend 75 minutes/week of vigorous aerobic exercise spread over 3 days per week (ie, 3 days per week for 25 to 30 minutes per session). HIGH followed double the guidelines of 150 minutes per week (ie, 3 days per week for 50 to 60 minutes per session). COMB followed the same aerobic exercise guideline as STAN plus a standard strength training program 3 days per week, consisting of two sets of 10 to 12 repetitions of nine different strength exercises at 60% to 75% of their estimated one repetition maximum. The strength exercises were leg extension, leg curl, leg press, calf raise, chest press, seated row, triceps extension, biceps curl, and modified curl-up. COMB completed about 30 to 35 minutes of strength exercise and 25 to 30 minutes of aerobic exercise for a combined total of 50 to 60 minutes of exercise.

Aerobic exercise could be completed on a cycle ergometer, treadmill, elliptical, rowing ergometer, or combination. Initial exercise intensity was individualized but generally began at 55% to 60% of peak oxygen consumption (VO_{2peak}) and progressed to

Table 1. Baseline Characteristics of CARE Trial Participants, Canada, 2008–2011*

Variable	Overall (n = 301)	STAN (n = 96)	HIGH (n = 101)	COMB (n = 104)
Demographic profile				
Age, y, mean (SD)	50.0 (8.9)	49.2 (8.4)	50.1 (8.8)	50.5 (9.4)
Married, No. (%)	194 (64.5)	59 (61.5)	64 (63.4)	71 (68.3)
Completed university, No. (%)	195 (64.8)	58 (60.4)	68 (67.3)	69 (66.3)
Income >$80 000/year, No. (%)	150 (54.3)	46 (52.3)	56 (58.3)	48 (52.2)
Sick leave, No. (%)	126 (41.9)	45 (46.9)	42 (41.6)	39 (37.5)
White ethnicity, No. (%)	255 (84.7)	82 (85.4)	86 (85.1)	87 (83.7)
Medical profile				
Weight, kg, mean (SD)	70.8 (15.2)	69.4 (13.2)	67.6 (13.2)	75.2 (17.7)
BMI, kg/m^2, mean (SD)	26.5 (5.5)	26.0 (4.9)	25.2 (4.5)	28.2 (6.5)
Obese, No. (%)	70 (23.3)	16 (16.7)	16 (15.8)	38 (36.5)
Disease stage, No. (%)				
I (T1N0)	101 (33.6)	28 (29.2)	38 (37.6)	35 (33.7)
IIa (T1N1,T2N0)	103 (34.2)	35 (36.5)	32 (31.7)	36 (34.6)
IIb (T2N1,T3N0)	66 (21.9)	21 (21.9)	18 (17.8)	27 (26.0)
IIIa (T1N2,T2N2,T3N1–2)	31 (10.3)	12 (12.5)	13 (12.9)	6 (5.8)
Surgical protocol, No. (%)				
Breast conservation	170 (56.5)	48 (50.0)	58 (57.4)	64 (61.5)
Chemotherapy category, No. (%)				
Any herceptin	50 (16.6)	18 (18.8)	16 (15.8)	16 (15.4)
No herceptin/any taxane	223 (74.1)	71 (74.0)	75 (74.3)	77 (74.0)
No herceptin/no taxane	28 (9.3)	7 (7.3)	10 (9.9)	11 (10.6)
Chemotherapy regimen, No. (%)				
FEC-D	101 (33.6)	26 (26.5)	40 (40.0)	35 (34.0)
TC/DC	71 (23.6)	23 (23.5)	21 (21.0)	27 (26.2)
TAC/DAC	30 (10.0)	11 (11.2)	11 (11.0)	8 (7.8)
AC-T	22 (7.3)	12 (12.2)	3 (3.0)	7 (6.8)
AC	18 (6.0)	5 (5.1)	7 (7.0)	6 (5.8)
TCH-DCT	16 (5.3)	6 (6.1)	5 (5.0)	5 (4.9)
FEC-DH	16 (5.3)	6 (6.1)	4 (4.0)	6 (5.8)
AC-TH	16 (5.3)	6 (6.1)	5 (5.0)	5 (4.9)
Other	11 (3.7)	3 (3.1)	4 (4.0)	4 (3.8)
Behavioral profile				
Aerobic exerciser, No. (%)	91 (30.2)	30 (31.3)	29 (28.7)	32 (30.8)
Resistance exerciser, No. (%)	64 (21.3)	21 (21.9)	19 (18.8)	24 (23.1)
Smoker, No. (%)	17 (5.6)	7 (7.3)	4 (4.0)	6 (5.8)

* Data are presented as the mean (standard deviation) for continuous variables and the number (percentage) for categorical variables. AC-T = adriamycin (doxorubicin), cyclophosphamide, paclitaxel, adriamycin (doxorubicin), cyclophosphamide; AC-TH = adriamycin (doxorubicin), cyclophosphamide, paclitaxel, herceptin (trastuzumab); BMI = body mass index; COMB = combined aerobic and resistance exercise program; FEC-D = fluorouracil (5FU), epirubicin, cyclophosphamide, docetaxel (taxotere); FEC-DH = fluorouracil (5FU), epirubicin, cyclophosphamide, docetaxel (taxotere), herceptin (trastuzumab); HIGH = high-volume aerobic exercise program; SD = standard deviation; STAN = standard aerobic exercise program; TAC (DAC) = docetaxel (taxotere), adriamycin (doxorubicin), cyclophosphamide; TC (DC) = docetaxel (taxotere), cyclophosphamide.

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Table 2. Effects of exercise dose and type on patient-reported physical health in breast cancer patients receiving chemotherapy, Canada, 2008–2011*

Physical health variables	Baseline Mean (SD)	Adjusted within-group change at follow-up Mean (95% CI)	Adjusted between-group differences at follow-up†		
			COMB vs STAN Mean (95% CI); *P*	HIGH vs STAN Mean (95% CI); *P*	HIGH vs COMB Mean (95% CI); *P*
Physical functioning					
STAN	49.9 (5.8)	−2.3 (−3.4 to −1.2)	+0.5 (−1.1 to 2.1); .52	+0.8 (−0.8 to 2.4); .30	+0.3 (−1.3 to 1.9); .70
HIGH	50.2 (6.6)	−1.5 (−2.6 to −0.4)			
COMB	50.2 (6.9)	−1.8 (−2.9 to −0.7)			
Role–physical					
STAN	39.4 (9.9)	−1.6 (−2.9 to −0.3)	+1.0 (−0.9 to 2.9); .29	+0.5 (−1.4 to 2.4); .60	−0.5 (−2.4 to 1.4); .59
HIGH	40.9 (10.7)	−1.1 (−2.4 to 0.2)			
COMB	40.6 (11.3)	−0.6 (−1.9 to 0.7)			
Bodily pain					
STAN	45.0 (9.0)	−1.4 (−2.7 to −0.1)	+0.3 (−1.5 to 2.1); .72	+2.3 (0.5 to 4.1); .02	+2.0 (0.1 to 3.8); .04
HIGH	46.9 (9.1)	+0.9 (−0.4 to 2.2)			
COMB	45.8 (9.1)	−1.1 (−2.3 to 0.2)			
General health					
STAN	51.1 (8.0)	−1.6 (−2.9 to −0.2)	−0.7 (−2.6 to 1.1); .44	+0.6 (−1.2 to 2.5); .50	+1.4 (−0.5 to 3.2); .14
HIGH	51.7 (7.8)	−0.9 (−2.2 to 0.4)			
COMB	50.2 (8.2)	−2.3 (−3.6 to −1.0)			
Physical component summary					
STAN	46.9 (7.4)	−3.6 (−4.7 to −2.5)	+0.4 (−1.2 to 1.9); .64	+1.6 (0.1 to 3.1); .04	+1.2 (−0.3 to 2.7); .10
HIGH	48.2 (8.1)	−2.0 (−3.1 to −0.9)			
COMB	47.9 (7.8)	−3.2 (−4.3 to −2.2)			
Trial outcome index–fatigue					
STAN	82.8 (14.9)	−11.2 (−14.0 to −8.4)	+0.4 (−3.5 to 4.2); .84	+3.4 (−0.5 to 7.2); .09	+3.0 (−0.8 to 6.8); .12
HIGH	82.8 (17.8)	−7.8 (−10.5 to −5.1)			
COMB	83.7 (18.5)	−10.8 (−13.5 to −8.1)			

* CI = confidence interval; COMB = combined aerobic and resistance exercise program; HIGH = high-volume aerobic exercise program; STAN = standard aerobic exercise program; SD = standard deviation.

† Follow-up is the average for midpoint 1, midpoint 2, and after intervention based on mixed model analysis. Analyses are adjusted for baseline value of the outcome, age, education, baseline exercise, body mass index, disease stage, surgery type, and chemotherapy protocol. The statistical test was linear mixed model analysis, and all *P* values are two-sided.

70% to 75% of VO_{2peak} by week 6. Initial exercise duration was also individualized but generally began between 15 to 30 minutes per session and achieved 25 to 30 minutes per session by week 4 (STAN and COMB) or 50 to 60 minutes per session by week 6 (HIGH). All exercise programs were supervised by qualified exercise physiologists. Unsupervised aerobic exercise was permitted but not encouraged.

Assessment of Primary and Secondary Endpoints

Patient-reported outcomes were assessed at baseline (usually before chemotherapy but always before the second cycle of chemotherapy), after one-third of chemotherapy, after two-thirds of chemotherapy, and after intervention (3 to 4 weeks after chemotherapy) with further follow-up at 6 months, 1 year, and 2 years (follow-up data not presented). The primary outcome was patient-reported physical functioning assessed by the physical functioning subscale of the Medical Outcomes Survey Short Form (SF)–36 (6). Important secondary outcomes were the other three physical component subscales of the SF-36 (role–physical, bodily pain, and general health), the physical component summary, the trial outcome index–fatigue (7), breast cancer symptoms (8), fatigue symptoms (7), taxane/neuropathy symptoms (9), and endocrine symptoms (10).

Health-related fitness was assessed at baseline, after intervention, and at 1-year follow-up (follow-up data not presented). Aerobic fitness was evaluated using a maximal incremental exercise protocol on a treadmill (11). Expired gases were analyzed using an automated metabolic measurement cart. VO_{2peak} was determined by taking the highest values during a 15-second period. Muscular strength was determined by an equation that used seven to 10 repetitions of a submaximal weight to estimate maximal strength (one repetition maximum) on the horizontal bench and leg press. Muscular endurance was assessed by the number of repetitions that could be completed using 50% of the estimated baseline one repetition maximum. Body weight and standing height were assessed without shoes using a balance beam scale (Health-o-Meter, Pelstar, LLC (McCook Illinois)). A dual x-ray absorptiometry scan was obtained for the assessment of whole body fat and lean tissue using a Lunar Prodigy (General Electric Company, Madison, WI) in Edmonton and Ottawa and a QDR 4500W (Hologic, Waltham, MA) in Vancouver with daily calibration. Chemotherapy completion was assessed as the average relative dose intensity for the originally planned regimen (12,13). Medical data were abstracted from records. Adverse events were reported by patients or observed by the exercise trainers.

Statistical Analyses and Sample Size Calculation

With 100 participants per group, our trial had 80% power to detect a standardized effect size (mean difference divided by standard deviation [SD]) of 0.44 for our primary outcome of patient-reported physical functioning using a two-tailed alpha of 0.025 that adjusted for our

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two primary comparisons of HIGH and COMB vs STAN. This effect size is consistent with the range of 0.33 to 0.50 suggested as meaningful for patient-reported outcomes (14). Linear mixed models were used to model each patient-reported outcome measure at the three post-randomization time points, assuming an unstructured correlation structure for the three-dimensional error term, and to compare the average mean differences between arms, assumed to be common across the three time points (15). Our primary analysis was adjusted for the baseline value of the outcome, age, education, previous exercise, body mass index, disease stage, surgery type, and chemotherapy protocol because of imbalances in these covariables and their possible associations with outcomes and adherence. We conducted intention-to-treat analyses using all available data even for participants with some missing data. All statistical tests were two-sided.

Results

Between April 2008 and September 2011, we randomized 301 of 728 (41.3%) eligible patients (Figure 1). We obtained patient-reported outcome data from questionnaires on 99.0% of patients at each point during and after chemotherapy. Baseline characteristics of the sample are presented in Table 1. The planned chemotherapy regimens ranged from 12 to 26 weeks with a mean of 16.3 weeks (SD = 3.2). The mean length of the exercise intervention was 16.4 weeks (SD = 3.6), resulting in an average of 49 (SD = 11) possible exercise sessions. STAN, HIGH, and COMB completed 87.8% (n = 43 of 49), 81.6% (n = 40 of 49), and 78.0% (n = 39 of 50) of their prescribed aerobic exercise sessions, respectively (P = .004), with 88.1% of the sessions supervised. Average duration of the aerobic exercise sessions was 28 (SD = 4), 48 (SD = 8), and 27 (SD = 3)

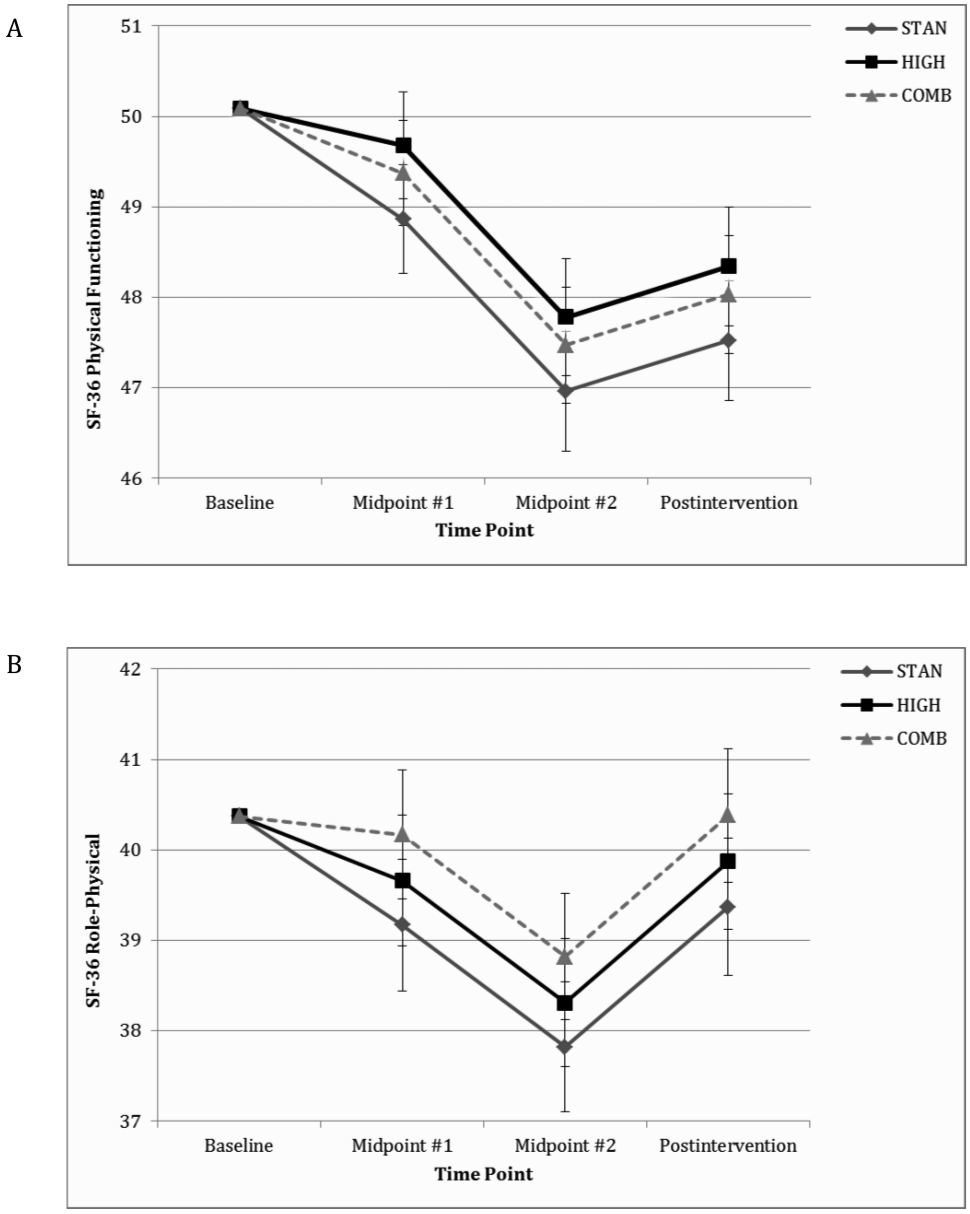

Figure 2. Effects of exercise dose and type on the following: physical functioning (**A**); role–physical (**B**); bodily pain (**C**); general health (**D**); physical component summary (**E**); and trial outcome index–fatigue (**F**). Means and standard errors are based on adjusted analyses. COMB = combined aerobic and resistance exercise program; HIGH = high-volume aerobic exercise program; STAN = standard aerobic exercise program.

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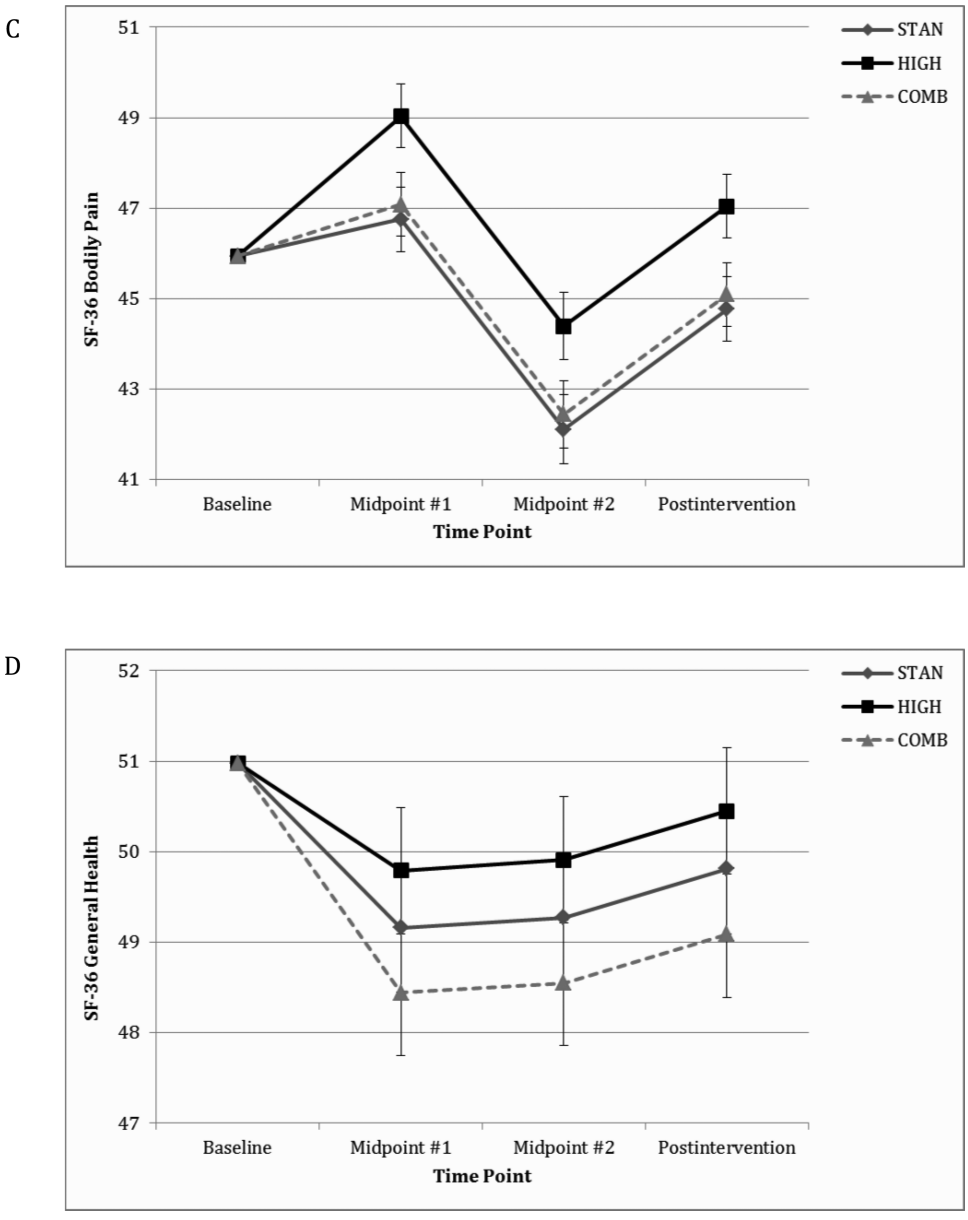

Figure 2. Continued

minutes, respectively, for STAN, HIGH, and COMB ($P < .001$), and the resulting average weekly minutes of aerobic exercise were 73 (SD = 17), 120 (SD = 39), and 64 (SD = 19) ($P < .001$). Average intensity of the aerobic exercise was 68.4% (6.5), 65.2% (7.8), and 67.4% (6.6) of VO_{2peak} for STAN, HIGH, and COMB, respectively ($P = .005$). COMB participants attended 66.0% (33 of 50) of their resistance exercise sessions and completed 98.2% or more of their prescribed weight, sets, and repetitions each session. Nonprotocol exercise was less than 10 minutes of vigorous exercise and less than 0.5 sessions of resistance exercise outside of the trial.

Patient-Reported Physical Functioning and Symptom Management

Neither HIGH (+0.8; 95% confidence interval [CI] = −0.8 to 2.4; $P = .30$) nor COMB (+0.5; 95% CI = −1.1 to 2.1; $P = .52$) were superior to STAN for the primary outcome of the SF-36 physical functioning subscale (Table 2; Figure 2). For the important secondary outcomes, HIGH was superior to STAN for the physical component summary (+1.6; 95% CI = 0.1 to 3.1; $P = .04$) and bodily pain (+2.3; 95% CI = 0.5 to 4.1; $P = .02$), and was borderline superior for the trial outcome index–fatigue (+3.4; 95% CI = −0.5 to 7.2; $P = .09$]. HIGH was also superior to COMB for bodily pain (+2.0; 95% CI = 0.1 to 3.8; $P = .04$) and borderline superior for the physical component summary (+1.2; 95% CI = −0.3 to 2.7; $P = .10$). For symptoms (Table 3; Figure 3), both HIGH (+2.2; 95% CI = 0.4 to 4.0; $P = .02$) and COMB (+2.5; 95% CI = 0.6 to 4.3; $P = .009$) were superior to STAN for endocrine symptoms, and HIGH was borderline superior to STAN for fatigue (+1.8; 95% CI = −0.3 to 4.0; $P = .10$).

Health-Related Fitness and Chemotherapy Completion Rate

For VO_{2peak}, HIGH was superior to COMB (+1.1; 95% CI = 0.1 to 2.1; $P = .03$) and borderline superior to STAN (+0.9; 95% CI = −0.1

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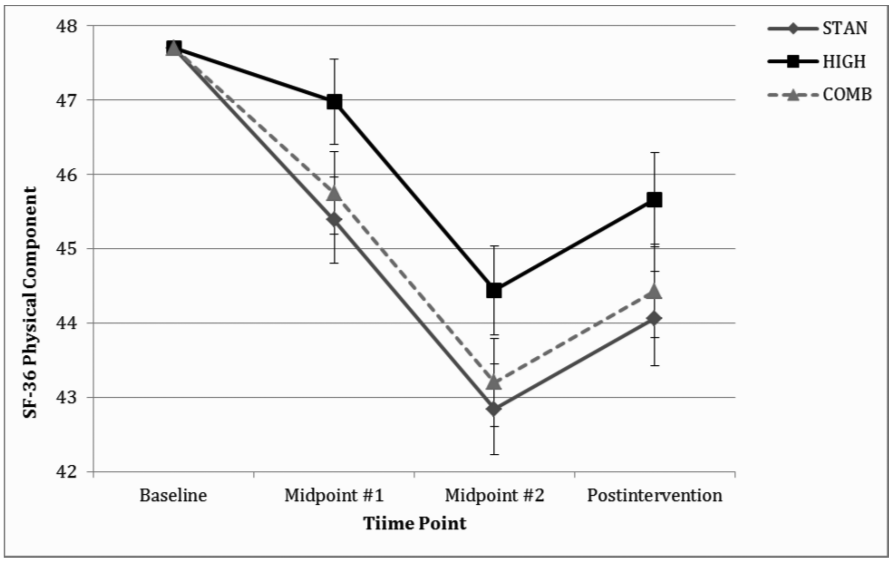

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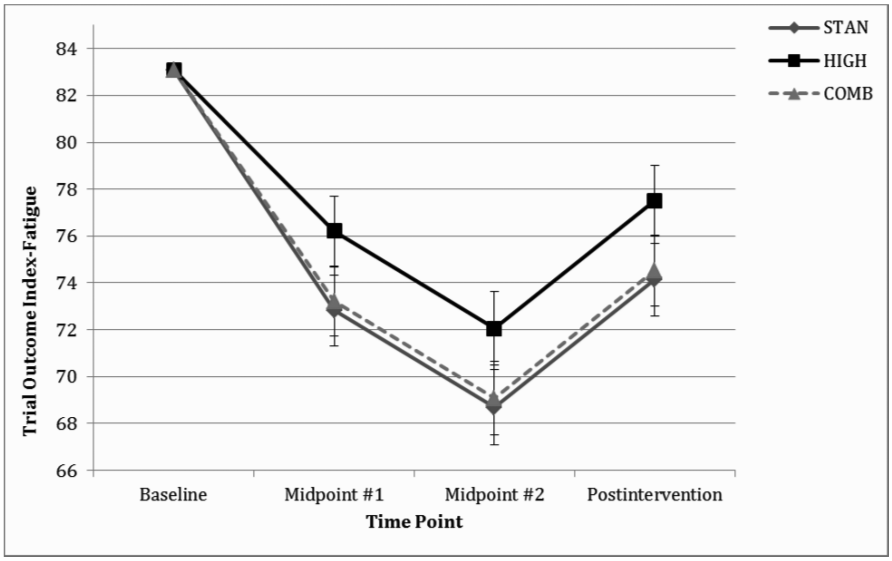

Figure 2. Continued

to 1.9; $P = .08$) (Table 4). COMB was superior to HIGH and STAN for upper body muscular strength (Ps < .001) and endurance (Ps < .001) and lower body muscular strength (Ps < .01) and endurance (Ps < .06) (Table 4). No differences were observed for body composition. Relative dose intensity was 93.9% in STAN compared with 92.7% in COMB and 91.6% in HIGH ($P = .34$). The percentage of participants who received 85% or more of their planned relative dose intensity was 87.5% in STAN, 85.6% in COMB, and 82.2% in HIGH ($P = .57$). No serious adverse events were related to exercise.

Discussion

Neither HIGH nor COMB were superior to STAN for the primary outcome of the SF-36 physical functioning subscale. Previous trials have shown that aerobic exercise and resistance exercise are superior to no exercise for improving patient-reported physical functioning in cancer patients receiving treatments (2). It is possible that additional aerobic exercise or weight training does not provide further benefit to patient-reported physical functioning during breast cancer chemotherapy. It is also possible, however, that the SF-36 physical functioning subscale is not sensitive to higher volumes of exercise in breast cancer patients receiving chemotherapy because of irrelevant items or ceiling effects related to their younger age and higher functioning. The SF-36 physical functioning subscale includes several low-level functioning items that are common activities of daily living that are not likely problematic for most breast cancer patients or may be adequately addressed by standard aerobic exercise. The SF-36 physical functioning subscale may be more sensitive to lifestyle interventions in older cancer survivors with lower functioning (16,17). The optimal patient-reported physical functioning scale for exercise trials in cancer patients is still unclear.

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Table 3. Effects of exercise dose and type on symptom management in breast cancer patients receiving adjuvant chemotherapy, Canada, 2008–2011*

Symptoms	Baseline Mean (SD)	Adjusted within-group change at follow–up Mean (95% CI)	Adjusted between-group differences at follow-up†		
			COMB vs STAN Mean (95% CI); *P*	HIGH vs STAN Mean (95% CI); *P*	HIGH vs COMB Mean (95% CI); *P*
Fatigue symptoms					
STAN	40.4 (9.3)	−7.0 (−8.6 to −5.5)	+0.8 (−1.3 to 3.0); .44	+1.8 (−0.3 to 4.0); .10	+1.0 (−1.2 to 3.1); .36
HIGH	40.6 (9.4)	−5.2 (−6.7 to −3.7)			
COMB	40.7 (10.2)	−6.2 (−7.7 to −4.7)			
Endocrine symptoms					
STAN	67.6 (7.2)	−7.2 (−8.5 to −5.8)	+2.5 (0.6 to 4.3); .009	+2.2 (0.4 to 4.0); .02	−0.3 (−2.1 to 1.6); .77
HIGH	67.5 (7.2)	−5.0 (−6.3 to −3.7)			
COMB	66.4 (7.6)	−4.7 (−6.0 to −3.4)			
Taxane symptoms					
STAN	61.0 (5.0)	−5.9 (−7.0 to −4.8)	+0.9 (−0.6 to 2.3); .23	+0.8 (−0.6 to 2.2); .25	0.0 (−1.4 to 1.4); .97
HIGH	61.4 (3.2)	−5.1 (−6.2 to −4.0)			
COMB	61.1 (4.4)	−5.1 (−6.2 to −4.0)			
Breast cancer symptoms					
STAN	25.9 (6.6)	−0.3 (−1.2 to 0.5)	+0.1 (−1.1 to 1.3); .82	+0.4 (−0.8 to 1.6); .54	+0.2 (−0.9 to 1.4); .69
HIGH	27.6 (6.2)	0.0 (−0.8 to 0.9)			
COMB	27.5 (5.7)	−0.2 (−1.0 to 0.6)			

* CI = confidence interval; COMB = combined aerobic and resistance exercise program; HIGH = high-volume aerobic exercise program; STAN = standard aerobic exercise program; SD = standard deviation.

† Follow-up is the average for midpoint 1, midpoint 2, and after intervention based on mixed model analysis. Analyses are adjusted for baseline value of the outcome, age, education, baseline exercise, body mass index, disease stage, surgery type, and chemotherapy protocol. The statistical test was linear mixed model analysis, and all *P* values are two-sided.

HIGH was superior to STAN for the more comprehensive SF-36 measure, the physical component summary, and trended toward superiority for the cancer-specific trial outcome index–fatigue scale. These data suggest the possibility of a dose–response effect for aerobic exercise. The mean group differences of 1.6 on the physical component summary and 3.4 on the trial outcome index–fatigue scale fall below the suggested meaningful group differences of two to three points (18) and five points (14), respectively; however, these modest effects were obtained over and above a standard aerobic exercise program. The comparison of higher-dose exercise programs with standard aerobic exercise provides the most rigorous test of the causal effects of exercise because it controls for the many nonexercise-related factors that may improve patient-reported outcomes, such as travel to the fitness center, interactions with the trainer or other participants, expectation of benefit, and cognitive dissonance.

Interestingly, HIGH even trended toward superiority over COMB for the SF-36 physical component summary scale, suggesting the possibility of an exercise type effect as well. It is unclear why additional aerobic exercise may have beneficial effects on patient-reported physical functioning but not additional weight training. It is possible that aerobic exercise better addresses central and leg fatigue, which may influence activities of daily living in breast cancer patients more so than upper-body (arm) fatigue. Previous trials in breast cancer survivors (19) and lymphoma patients (20) have found improvements in patient-reported physical functioning to be mediated by improved aerobic fitness.

HIGH was also superior to both STAN and COMB for bodily pain. Pain is a common symptom in breast cancer patients and is associated with anxiety, sleep disturbance, and poor quality of life (21). Few exercise trials in breast cancer patients have examined pain as an outcome (2). The mean group differences of 2.0 and 2.3 are within the suggested meaningful group differences of two to three points on SF-36 bodily pain scale (16). These results suggest both an exercise dose and type effect for aerobic exercise. Mechanisms for pain reduction from aerobic exercise may include endorphin production, weight loss, improved functioning, and mood (22).

Both HIGH and COMB were superior to STAN for managing endocrine symptoms. Endocrine symptoms are common and distressing in breast cancer patients (23), yet no previous exercise study has examined endocrine symptoms in breast cancer patients (2). Exercise may manage endocrine symptoms by increasing hypothalamic and peripheral β-endorphin production, which may stabilize the thermoregulatory center and reduce the risk of hot flashes (24). The endocrine symptom subscale has no minimal important difference, but the mean group differences of 2.5 and 2.2 translate into about 0.33 standard deviations. Our results suggest a dose–response effect of exercise regardless of exercise type. This finding may portend an even more powerful effect of exercise on endocrine symptoms when compared with no exercise and may be particularly important given the reluctance to prescribe hormone replacement therapy for menopausal symptoms in breast cancer patients (23).

Higher dose aerobic exercise partially blunted a substantial decline in maximal oxygen consumption in STAN and COMB by about 1.0 mL/mg/kg or 3% to 4%. These declines, despite aerobic exercise training, are even larger than previously reported in our Supervised Trial of Aerobic versus Resistance Training (START). These differences may be the result of changing chemotherapy protocols (26). During the START Trial (2002 to 2005), about 30% of patients received taxane-based chemotherapies, whereas in the CARE Trial (2008 to 2011), 90% of patients received such therapies.

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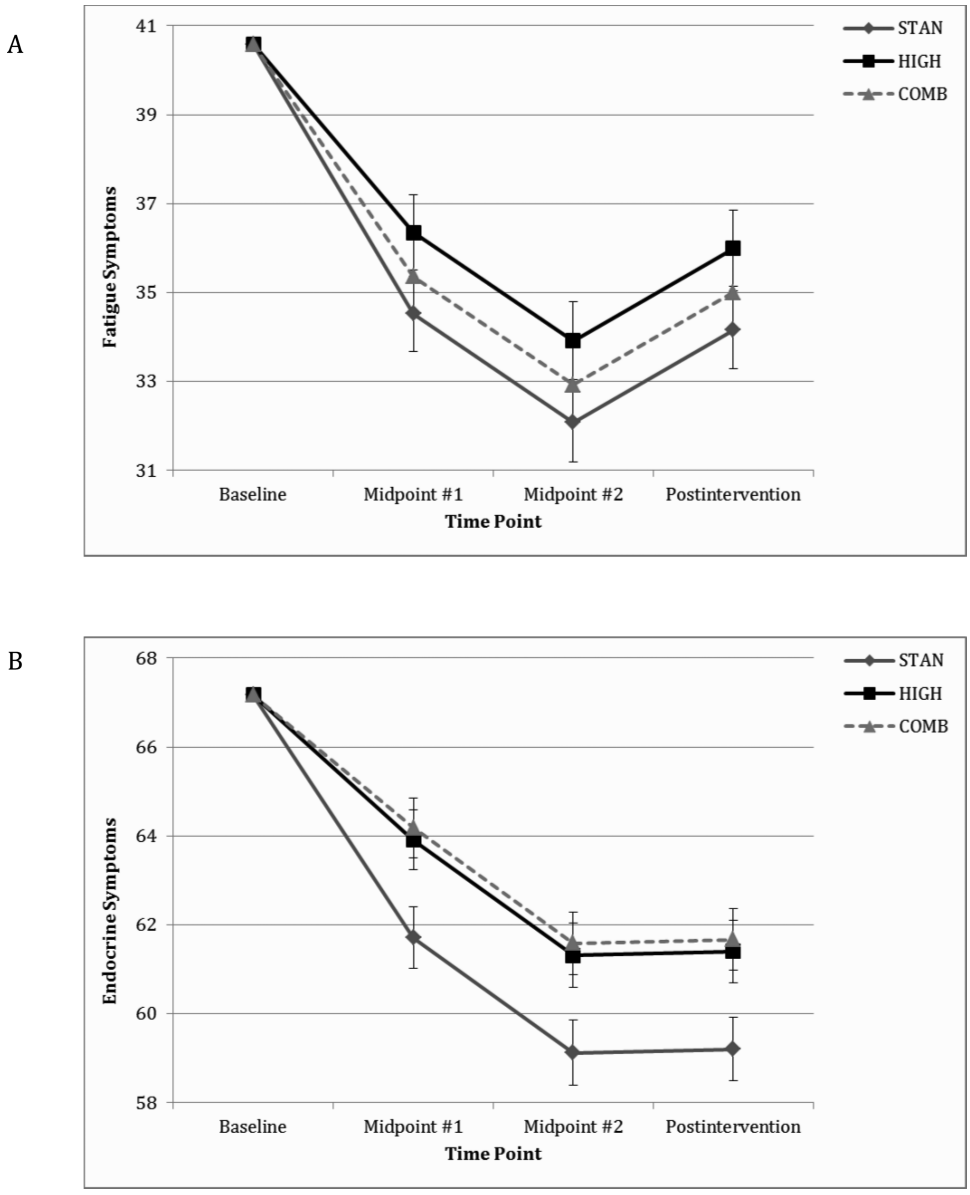

Figure 3. Effects of exercise dose and type on the following: fatigue symptoms (**A**); endocrine symptoms (**B**); taxane symptoms (**C**); and breast cancer symptoms (**D**). Means and standard errors are based on adjusted analyses. COMB = combined aerobic and resistance exercise program; HIGH = high-volume aerobic exercise program; STAN = standard aerobic exercise program.

Weight training improved muscular fitness compared with the aerobic exercise groups by approximately 10% to 30%. Again, in the START Trial we found that a similar weight training protocol improved muscular strength by approximately 35% compared with no exercise (25). The more modest improvements in the CARE trial may be the result of the aerobic exercise comparison groups or the changing chemotherapy protocols. In subgroup analyses from the START Trial, we found a strength improvement of 40% in patients not receiving taxane-based chemotherapies compared with 15% in patients receiving taxane-based chemotherapies (26). These data highlight the importance of tracking chemotherapy protocols in exercise trials because they may influence the exercise response.

There were no exercise dose or type effects on chemotherapy completion rate. We previously reported that weight training improved chemotherapy completion rate compared with usual care in breast cancer patients receiving chemotherapy (25). It is possible that the addition of weight training did not improve chemotherapy completion in the CARE trial because of the marginal beneficial effects of aerobic exercise or because the chemotherapy protocols have changed. Nevertheless, the CARE data suggest that even higher volumes of aerobic or combined exercise do not interfere with breast cancer patients' ability to complete their chemotherapy.

Our detailed exercise adherence data provide important information for the design of future exercise trials and clinical interventions. Although both of the higher-dose exercise groups completed more exercise than the standard group, relative adherence to the frequency and volume (minutes) of aerobic exercise was higher for STAN compared with HIGH and COMB. Moreover, STAN and COMB achieved slightly better adherence to the intensity

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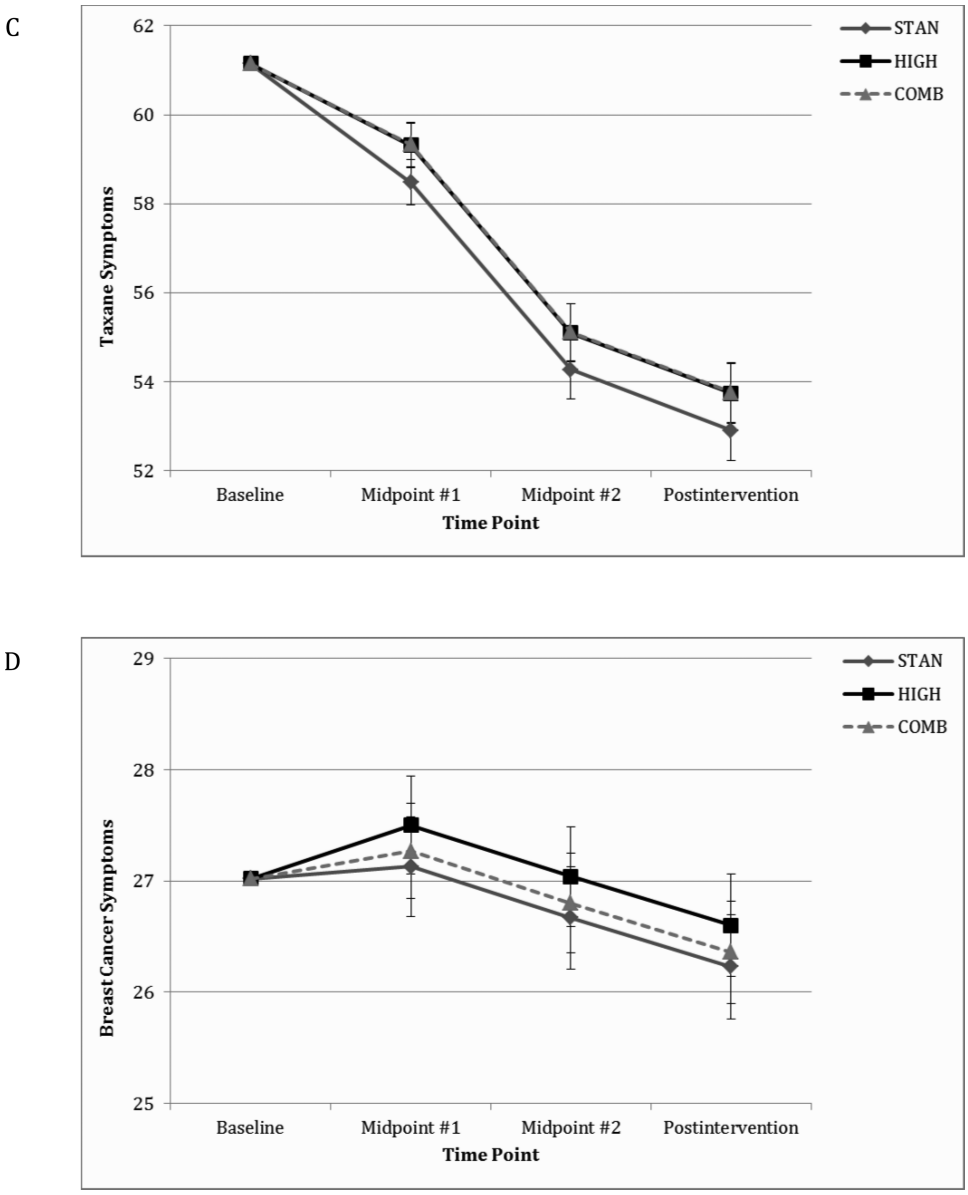

Figure 3. Continued

component of aerobic exercise than HIGH. Finally, COMB adhered better to their aerobic exercise prescription than strength exercise prescription because of the possibility of completing aerobic exercise at home. These relative adherence differences may partly explain the modest effects of our higher-dose exercise interventions, especially the COMB intervention, compared with the standard dose. Moreover, these differences also suggest that the higher-dose interventions are more challenging and may not achieve their full effects in clinical practice because of feasibility issues.

Our trial's strengths include the innovative design that simultaneously examined exercise dose and type effects, the clinical utility of these comparisons, the largest sample size to date, the well-defined population, the multicenter recruitment, the supervised exercise, the good adherence rates, the validated measures at multiple time points, and trivial loss-to-follow-up.

Limitations include the 41% recruitment rate, the demographically homogenous sample, the failure to collect data on decliners to determine selection biases and generalizability, and the adherence differences across groups that may have partly diluted the effects of the higher-dose interventions. Finally, given the 27 comparisons we made for the secondary patient-reported outcomes without adjustment for multiple testing, we would expect one or two false discoveries by chance if all of these comparisons were actually null.

In summary, a higher dose of aerobic or combined exercise compared with a standard dose of aerobic exercise did not dampen the impact of chemotherapy on patient-reported physical functioning as assessed by the SF-36 physical functioning subscale. The CARE Trial did demonstrate that higher doses of aerobic or combined exercise of up to 50 to 60 minutes per session are safe and feasible and do not interfere with chemotherapy completion or exacerbate any symptoms. Moreover, a higher dose of aerobic exercise curbs some of the negative impact of chemotherapy on aerobic fitness, patient-reported physical functioning, bodily pain, fatigue, and endocrine symptoms, whereas combined exercise improves

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Table 4. Effects of exercise dose and type on health-related fitness in breast cancer patients receiving adjuvant chemotherapy, Canada, 2008–2011*

Fitness variables	Baseline Mean (SD)	Adjusted within-group change at postintervention Mean (95% CI)	Adjusted between-group differences at postintervention		
			COMB vs STAN Mean (95% CI); *P*	HIGH vs STAN Mean (95% CI); *P*	HIGH vs COMB Mean (95% CI); *P*
VO_{2peak}, mL/kg/min					
STAN	29.0 (6.4)	−3.4 (−4.1 to −2.7)	−0.2 (−1.2 to 0.8); .70	+0.9 (−0.1 to 1.9); .08	+1.1 (0.1 to 2.1); .03
HIGH	28.9 (6.4)	−2.5 (−3.2 to −1.8)			
COMB	27.5 (6.4)	−3.6 (−4.3 to −2.9)			
Upper body strength, kg					
STAN	23.3 (8.5)	+1.7 (0.7 to 2.7)	+4.0 (2.5 to 5.4); .001	−1.7 (−3.1 to −0.3); .02	−5.7 (−7.1 to −4.3); .001
HIGH	23.0 (8.4)	0.0 (−1.0 to 1.0)			
COMB	25.0 (8.6)	+5.7 (4.7 to 6.7)			
Lower body strength, kg					
STAN	83.7 (24.2)	+2.5 (−0.7 to 5.8)	+6.0 (1.4 to 10.7); .01	0.0 (−4.6 to 4.6); .99	−6.0 (−10.7 to −1.4); .01
HIGH	77.6 (24.7)	+2.5 (−0.7 to 5.7)			
COMB	87.1 (27.4)	+8.6 (5.3 to 11.8)			
Upper body endurance, repetitions					
STAN	29.6 (16.0)	− 0.5 (−3.2 to 2.2)	+6.5 (2.7 to 10.3); .001	−2.9 (−6.7 to 1.0); .14	−9.4 (−13.2 to −5.6); .001
HIGH	25.9 (8.0)	− 3.4 (−6.1 to −0.7)			
COMB	26.8 (8.9)	+6.0 (3.3 to 8.6)			
Lower body endurance, repetitions					
STAN	55.8 (31.0)	+6.2 (−0.6 to 13.0)	+9.3 (−0.4 to 19.0); .06	−4.2 (−13.7 to 5.3); .38	−13.5 (−23.1 to −3.9); .006
HIGH	54.3 (25.0)	+2.0 (−4.6 to 8.6)			
COMB	56.7 (32.5)	+15.5 (8.7 to 22.3)			
Body weight, kg					
STAN	69.3 (13.1)	+1.6 (0.8 to 2.4)	−0.3 (−1.4 to 0.8); .57	−0.2 (−1.3 to 0.9); .68	+0.1 (−1.0 to 1.2); .86
HIGH	67.2 (13.3)	+1.4 (0.6 to 2.1)			
COMB	74.7 (17.4)	+1.3 (0.5 to 2.0)			
Lean mass, kg					
STAN	40.3 (5.7)	+0.9 (0.6 to 1.3)	0.0 (−0.5 to 0.6); .86	−0.2 (−0.7 to 0.3); .35	−0.3 (−0.8 to 0.2); .26
HIGH	39.7 (5.3)	+0.7 (0.4 to 1.1)			
COMB	41.2 (6.1)	+1.0 (0.6 to 1.3)			
Fat mass, kg					
STAN	25.7 (9.4)	+0.7 (0.2 to 1.3)	−0.4 (−1.2 to 0.4); .38	−0.2 (−1.0 to 0.6); .61	+0.2 (−0.6 to 0.9); .70
HIGH	24.3 (9.8)	+0.5 (−0.0 to 1.1)			
COMB	29.7 (12.3)	+0.4 (−0.2 to 0.9)			
Body fat, %					
STAN	37.5 (8.1)	+0.2 (−0.4 to 0.7)	−0.3 (−1.1 to 0.5); .44	−0.3 (−1.1 to 0.5); .47	0.0 (−0.7 to 0.8); .96
HIGH	36.4 (8.4)	− 0.1 (−0.6 to 0.4)			
COMB	39.9 (9.0)	− 0.1 (−0.7 to 0.4)			

* Analyses are adjusted for baseline value of the outcome, age, education, baseline exercise, body mass index, disease stage, surgery type, and chemotherapy protocol. The statistical test was linear mixed model analysis, and all *P* values are two-sided. CI = confidence interval; COMB = combined aerobic and resistance exercise program; HIGH = high-volume aerobic exercise program; SD = standard deviation; STAN = standard aerobic exercise program; VO_{2peak} = peak volume of oxygen consumed.

muscular fitness and partly mitigates the worsening of endocrine symptoms. Additional exercise dose and type trials targeting these specific outcomes are warranted. Cancer care professionals can safely recommend higher doses of exercise during breast cancer chemotherapy in appropriately supervised settings.

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Notes

KS Courneya had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. KS Courneya, DC McKenzie, JR Mackey, K. Gelmon, CM Friedenreich, Y. Yasui, RD Reid, and RJ Segal were responsible for the study concept and design. KS Courneya, DC McKenzie, JR Mackey, K. Gelmon, CM Friedenreich, Y. Yasui, RD Reid, D. Cook, D. Jespersen, C. Proulx, LB Dolan, CC Forbes, E. Wooding, L. Trinh, and RJ Segal were responsible for the analysis and interpretation of data. KS Courneya was responsible for the drafting of the manuscript. KS Courneya, DC McKenzie, JR Mackey, K. Gelmon, CM Friedenreich, Y. Yasui, RD Reid, D. Cook, D. Jespersen, C. Proulx, LB Dolan, CC Forbes, E. Wooding, L. Trinh, and RJ Segal were responsible for critical revision of the manuscript for important intellectural content. KS Courneya and Y. Yasui were responsible for statistical analysis. KS Courneya, DC McKenzie, JR Mackey, K. Gelmon, CM Friedenreich, Y. Yasui, RD Reid, and RJ Segal obtained funding. KS Courneya, DC McKenzie, JR Mackey, K. Gelmon, CM Friedenreich, Y. Yasui, RD Reid, D. Cook, D. Jespersen, C. Proulx, LB Dolan, CC Forbes, E. Wooding, L. Trinh, and RJ Segal provided administrative, technical, or material support.

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