Research Article

Cancer Epidemiology, Biomarkers & Prevention

A Multicenter Randomized Trial of the Effects of Exercise Dose and Type on Psychosocial Distress in Breast Cancer Patients Undergoing Chemotherapy

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Abstract

Background: Exercise may improve psychosocial distress in patients with cancer; however, few studies have examined the effects of different types or doses of exercise, or whether exercise effects are related to baseline depression levels.

Methods: In a multicenter trial in Canada, we randomized 301 patients with breast cancer initiating chemotherapy to thrice weekly, supervised exercise 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 depression assessed by the Center for Epidemiological Studies-Depression scale at baseline, twice during chemotherapy, and postchemotherapy. Secondary endpoints were anxiety, perceived stress, and self-esteem.

Results: Repeated measures ANOVA indicated that neither HIGH [mean difference = −0.9; 95% confidence interval (CI), +0.0 to −1.8; $P = 0.061$] nor COMB (mean difference = −0.4; 95% CI, +0.5 to −1.3; $P = 0.36$) was superior to STAN for managing depressive symptoms. In a planned subgroup analysis, there was a significant interaction with baseline depression levels ($P_{\text{interaction}} = 0.027$) indicating that COMB and HIGH were effective for managing depressive symptoms in patients with clinical levels of depressive symptoms at baseline.

Conclusions: Compared with a standard volume of aerobic exercise, higher volumes of exercise did not help manage depressive symptoms in unselected patients with breast cancer receiving chemotherapy, but they were effective in patients with clinical levels of depressive symptoms at baseline.

Impact: A phase III exercise trial targeting depressed patients with breast cancer is warranted. *Cancer Epidemiol Biomarkers Prev; 23(5); 857–64. ©2014 AACR.*

Introduction

Depression is the most common psychologic symptom in patients with cancer (1) and occurs more often in patients with cancer than the general population (2), suggesting that the disease and/or its treatments may cause or exacerbate depression. Depression in patients with cancer may lead to longer hospital stays, physical distress, poorer treatment compliance, lower quality of life (3), and even shorter survival (4, 5). Both psychosocial and pharmacologic interventions have been shown to be efficacious for treating depression; however, these interventions are not safe, acceptable, or effective for all patients with cancer (6, 7).

Exercise is known to have antidepressive effects in healthy and clinically depressed populations (8, 9) but these effects may not generalize to patients with cancer because of the etiology related to the disease and treatments. Moreover, the quality of the evidence on exercise and depression in patients with cancer has been modest. Several recent systematic reviews have concluded that exercise training provides a small reduction in depressive symptoms in cancer survivors (10, 11) and in patients with breast cancer undergoing adjuvant therapy (12). Unfortunately, these reviews have also noted major methodologic limitations in these trials, inconsistent evidence concerning a dose–response effect, and the inclusion of few depressed patients with cancer. The significance of this last limitation is highlighted by a recent systematic review of psychosocial interventions in patients with cancer (13) that clearly showed that the beneficial effects

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doi: 10.1158/1055-9965.EPI-13-1163

of psychosocial interventions on depression are strongly related to baseline distress. Here, we report what we believe to be the largest exercise trial to date to examine depression in patients with cancer; the first to examine exercise dose and type effects, and the first to examine whether the effects of exercise on depression are related to baseline depression levels.

The Combined Aerobic and Resistance Exercise (CARE) Trial (14) addressed the exercise dose versus type question in patients with breast cancer receiving chemotherapy by comparing a thrice weekly 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). Moreover, given the large sample size ($N = 301$), we were able to perform subgroup analyses to directly test whether exercise effects are related to baseline depression levels. On the basis of systematic reviews in exercise oncology suggesting that a higher weekly volume of exercise is associated with a greater reduction in depressive symptoms (10–12), we hypothesized that our higher dose exercise interventions (HIGH and COMB) would be superior to STAN in reducing depressive symptoms. Moreover, based on a systematic review in psychosocial oncology (13), we hypothesized that the magnitude of the effect would be larger for patients with breast cancer with clinical levels of depressive symptoms at baseline. Finally, we examined other potential moderators of the intervention effect to inform future research and clinical practice.

Materials and Methods

Setting and participants

The CARE Trial methods have been reported elsewhere (14). Briefly, the CARE Trial was a multicenter Canadian trial with sites in Edmonton, Ottawa, and Vancouver. Ethics approval was received from all centers and consent obtained from all participants. Eligibility criteria included English or French speaking nonpregnant women $\geq$18 years old with stage I–IIIc breast cancer initiating adjuvant chemotherapy. Women were excluded if they had incomplete axillary surgery, transabdominal rectus abdominus muscle reconstructive surgery, significant health problems, or were not approved by their oncologist. Eligible participants were identified by their treating oncologist before chemotherapy.

Randomization

After baseline assessments, participants were stratified by center and chemotherapy protocol (any Herceptin versus no Herceptin/any taxane versus no Herceptin/no taxane) and randomly assigned in a 1:1:1 ratio to STAN, COMB, or HIGH using a computer-generated program. The allocation sequence was generated in Edmonton and concealed from the project directors who assigned participants to groups.

Exercise training interventions

The exercise training interventions have been described elsewhere (14). Briefly, participants exercised for the duration of their chemotherapy schedule. STAN followed the Physical Activity Guidelines for Americans (15) which have been endorsed for cancer survivors (16, 17). These guidelines recommend a minimum of 75 minutes/week of vigorous aerobic exercise spread over 3 days/week (i.e., 25–30 minutes/session). HIGH followed double the minimum guidelines of 150 minutes/week of vigorous aerobic exercise per week (i.e., 50–60 minutes/session). COMB followed the same aerobic exercise guideline as STAN plus a standard strength training program for 3 days/week (i.e., about 50–60 minutes of combined exercise). For each supervised exercise session, exercise trainers recorded the attendance, duration, and intensity of aerobic exercise, and the amount of weight and number of sets and repetitions for each strength exercise.

Assessment of primary and secondary psychosocial endpoints

Psychosocial distress was assessed at four time points: baseline (usually before chemotherapy), about one third and two thirds through chemotherapy, and postchemotherapy (3–4 weeks after chemotherapy). The primary psychosocial distress endpoint, depression, was assessed by a 10 item short-form version (18) of the original 20 item Center for Epidemiological Studies-Depression Scale (CES-D; ref. 19) that has been validated in patients with breast cancer (20). The CES-D measures the frequency of depressive symptoms over the past week on a 0 to 3 scale and is summed to obtain a total score ranging from 0 to 30. Higher scores indicate more depressive symptoms. Secondary psychosocial distress endpoints were anxiety as assessed by the 10 item short form of the Spielberger State Anxiety Inventory (21), perceived stress as assessed by the Perceived Stress Scale (22), and self-esteem as assessed by the Rosenberg Self-Esteem Scale (23).

Selection and assessment of moderators

Baseline depression level was our primary moderator of interest and was derived by dividing patients into "clinical levels of depressive symptoms" and "subclinical levels of depressive symptoms" using a cutoff score of ≥ 8 on the 10 item CES-D based on the $\geq$ 16 cutoff score recommended for the 20 item scale (19). We also selected nine other moderators based on their scientific plausibility, clinical utility, and support in previous research (24, 25). The moderators consisted of age (<50 years vs. $\geq$ 50 years), marital status (married vs. not married), meeting aerobic exercise guidelines at baseline (< vs. $\geq$ 150 minutes of exercise/week), meeting strength exercise guidelines at baseline (< vs. $\geq$ two sessions/week), number of comorbidities (0 vs. $\geq$ 1), disease stage (stages I/IIa vs. stages IIb/III), type of surgery (lumpectomy vs. mastectomy), chemotherapy protocol (taxane vs. no taxane), and body mass index (nonobese <29.9 kg/m^2 vs. obese $\geq$ 30 kg/m^2).

Table 1. Baseline distribution of proposed moderators in the CARE Trial, Canada, 2008–2011

Variable	Overall ($N = 296$)	Standard ($n = 95$)	High ($n = 99$)	Combined ($n = 102$)
Baseline depression, No. (%)				
Depressed	93 (31.4%)	25 (26.3%)	32 (32.3%)	36 (35.3%)
Not depressed	203 (68.6%)	70 (73.7%)	67 (67.7%)	66 (64.7%)
Age, No. (%)				
<50 y	148 (50.0%)	50 (52.6%)	55 (55.6%)	43 (42.2%)
≥ 50 y	148 (50.0%)	45 (47.4%)	44 (44.4%)	59 (57.8%)
Marital status				
Married	192 (64.9%)	59 (62.1%)	63 (63.6%)	70 (68.6%)
Not married	104 (35.1%)	36 (37.9%)	36 (36.4%)	32 (31.4%)
Disease stage, No. (%)				
I/IIa	203 (68.6%)	62 (65.3%)	70 (70.7%)	71 (69.6%)
IIb/IIIa	93 (31.4%)	33 (34.7%)	29 (29.3%)	31 (30.4%)
Surgical protocol, No. (%)				
Lumpectomy	167 (56.4%)	47 (49.5%)	57 (57.6%)	63 (61.8%)
Mastectomy	129 (43.6%)	48 (50.5%)0	42 (42.4%)	39 (38.2%)
Chemotherapy regimen, No. (%)				
Taxanes	268 (90.5%)	88 (92.6%)	88 (88.9%)	92 (90.2%)
No taxanes	28 (9.5%)	7 (7.4%)	11 (11.1%)	10 (9.8%)
Comorbidities, No. (%)				
None	132 (44.6%)	49 (51.6%)	45 (45.5%)	38 (37.3%)
≥ 1	164 (55.4%)	46 (48.4%)	54 (54.5%)	64 (62.7%)
Baseline aerobic exercise, No. (%)				
Not meeting guidelines	207 (69.9%)	66 (69.5%)	71 (71.7%)	70 (68.6%)
Meeting guidelines	89 (31.1%)	29 (30.5%)	28 (28.3%)	32 (31.4%)
Baseline strength exercise, No. (%)				
Not meeting guidelines	234 (79.1%)	75 (78.9%)	81 (81.8%)	78 (76.5%)
Meeting guidelines	62 (20.9%)	20 (21.1%)	18 (18.2%)	24 (23.5%)
Body mass index, No. (%)				
Nonobese	227 (76.7%)	79 (83.2%)	84 (84.8%)	64 (62.7%)
Obese	69 (23.3%)	16 (16.8%)	15 (15.2%)	38 (37.3%)

Data analyses

The CARE trial randomized 100 participants per group to achieve 80% power to detect a standardized effect size (mean difference divided by SD) of about 0.40 for patient-reported outcomes using a two-tailed α of 0.05. This effect size is consistent with the range of 0.33 to 0.50 that is suggested as meaningful for patient-reported outcomes (26). Repeated measures ANOVA were used to test the main effects as well as interaction effects, and the assumption of homogeneity of variance was tested and met across groups for each outcome at each time point. We modeled each outcome at the three postrandomization time points (one third through chemotherapy, two thirds through chemotherapy, and postchemotherapy) to compare the average mean differences among the three arms, assumed to be common across the three time points (27). 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 except when a covariate was tested as the moderator. For all analyses, we used the intention-to-treat principle and included all participants with complete follow-up data.

Results

Participant flow through the trial has been reported elsewhere (14). Briefly, we randomized 301 of 728 (41%) eligible patients between April 2008 and September 2011. We obtained psychosocial distress data on 299 (99.3%) patients at midpoint #1, 298 (99.0%) at midpoint #2, and 298 (99.0%) at postintervention with complete data on 296 (98.3%) patients. The distribution of the proposed moderators is reported in Table 1. The baseline mean depression score was 5.9 (SD = 4.7) with 93 (31.4%) patients categorized as having clinical levels of depressive symptoms at baseline. Adherence to the exercise interventions is reported elsewhere (14). Briefly, STAN, HIGH, and COMB completed 88%, 82%, and 78% of their aerobic exercise sessions with an average duration of 28 (SD = 4), 48 (SD = 8), and 27 (SD = 3) minutes, respectively. Average intensity was 68.4% (6.5), 65.2% (7.8), and 67.4% (6.6) of VO_{2peak} for STAN, HIGH, and COMB,

Table 2. Effects of exercise dose and type on psychosocial functioning in patients with breast cancer receiving chemotherapy, Canada, 2008–2011

	Baseline M (SD)	Adjusted mean follow-up score[a,b] M (SE)	Adjusted between group differences during follow-up[a,b] COMB vs. STAN M (95% CI); *P*	HIGH vs. STAN M (95% CI); *P*	HIGH vs. COMB M (95% CI); *P*
Depression (0–30)					
STAN	5.6 (3.9)	6.8 (0.33)	−0.4 (+0.5 to −1.3); 0.36	−0.9 (+0.0 to −1.8); 0.061	−0.4 (+0.5 to −1.4); 0.34
HIGH	6.3 (5.1)	5.9 (0.33)	—	—	—
COMB	5.8 (5.0)	6.4 (0.32)	—	—	—
Anxiety (10–40)					
STAN	20.4 (6.6)	18.4 (0.40)	−0.5 (+0.6 to −1.6); 0.35	−1.0 (+0.1 to −2.1); 0.084	−0.4 (+0.7 to −1.5); 0.43
HIGH	20.6 (5.9)	17.4 (0.39)	—	—	—
COMB	19.6 (7.3)	17.9 (0.39)	—	—	—
Perceived stress (0–56)					
STAN	20.4 (8.0)	21.0 (0.6)	−0.7 (+0.9 to −2.3); 0.41	+0.4 (+2.0 to −1.2); 0.59	+1.1 (+2.7 to −0.5); 0.17
HIGH	19.4 (8.1)	21.4 (0.6)	—	—	—
COMB	19.2 (8.5)	20.3 (0.6)	—	—	—
Self-esteem (10–40)					
STAN	33.5 (4.3)	34.8 (0.29)	−0.9 (−0.1 to −1.7); 0.033	−0.3 (+0.5 to −1.1); 0.51	+0.6 (−0.2 to +1.4); 0.14
HIGH	34.3 (5.2)	34.5 (0.28)	—	—	—
COMB	34.0 (5.2)	33.9 (0.28)	—	—	—

[a]Follow-up score is the average for midpoint #1, midpoint #2, and postintervention based on repeated measures analyses.
[b]Analyses are adjusted for baseline value of the outcome, age, education, baseline exercise, comorbidities, body mass index, disease stage, surgery type, and chemotherapy protocol.

respectively. COMB completed 66% (33/50) of their strength sessions and ≥ 98% of their prescribed weight, sets, and repetitions each session.

Main effects of exercise dose and type on psychosocial distress

Table 2 reports the main effects of the exercise interventions on psychosocial distress averaged across the three postrandomization time points. Figure 1A–D depicts the pattern of intervention effects separately across the three postrandomization time points. Neither HIGH [mean group difference = −0.9; 95% confidence interval (CI), +0.0 to −1.8; $P = 0.061$; $d = -0.19$) nor COMB (mean group difference = −0.4; 95% CI, +0.5 to −1.3; $P = 0.36$; $d = -0.09$) was statistically superior to STAN for managing depressive symptoms. There were also no differences in anxiety or perceived stress. STAN was superior to COMB for self-esteem (mean group difference = 0.9; 95% CI, 0.1 to 1.7; $P = 0.033$; $d = 0.18$).

Moderators of the effects of exercise dose and type on depression

Baseline level of depressive symptoms demonstrated a statistically significant interaction with group assignment ($P_{interaction} = 0.027$; Fig. 2A). In subgroup analyses of patients with clinical levels of depressive symptoms at baseline ($n = 93$), COMB was superior to STAN (mean group difference = −2.2; 95% CI, −0.1 to −4.3; $P = 0.039$; $d = -0.47$) and HIGH was borderline superior to STAN (mean group difference = −1.9; 95% CI, +0.2 to −4.0; $P = 0.077$; $d = -0.40$). No differences emerged for patients with subclinical levels of depressive symptoms at baseline ($n = 203$). There was also a statistically significant interaction for baseline strength exercise ($P_{interaction} = 0.041$; Fig. 2B). For patients who were not meeting strength exercise guidelines at baseline ($n = 234$), HIGH was superior to both STAN (mean group difference = −1.2; 95% CI, −0.1 to −2.2; $P = 0.026$; $d = -0.26$) and COMB (mean group difference = −1.0; 95% CI, −0.0 to −2.1; $P = 0.046$; $d = -0.21$). For patients who were meeting strength exercise guidelines at baseline ($n = 62$), COMB was borderline superior to HIGH (mean group difference = −1.9; 95% CI, +0.1 to −4.0; $P = 0.067$; $d = -0.40$). Finally, there was a statistically significant interaction for chemotherapy regimen ($P_{interaction} = 0.024$; Fig. 2C). For patients who were not receiving taxanes ($n = 28$), HIGH was superior to STAN (mean group difference = −3.0; 95% CI, −0.1 to −6.0; $P = 0.046$; $d = -0.64$). For patients who were receiving taxanes ($n = 268$), there were no differences among the groups. No significant interactions were observed for age, marital status, meeting aerobic exercise guidelines at baseline, number of comorbidities, disease stage, type of surgery, and body mass index.

Discussion

Neither a higher dose of aerobic exercise nor combined exercise was statistically superior to a standard dose of

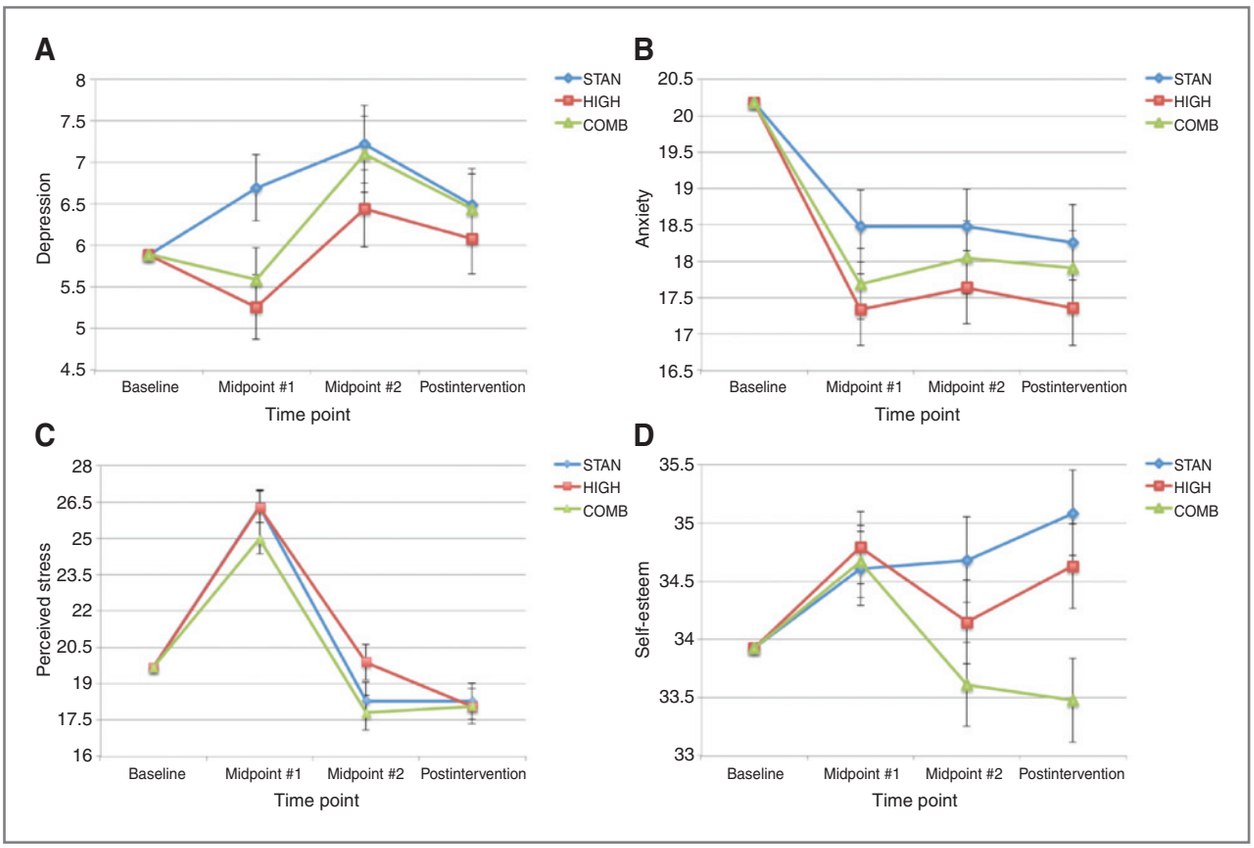

Figure 1. Effects of exercise dose and type on depression (A), anxiety (B), perceived stress (C), and self-esteem (D) during and after breast cancer chemotherapy. Mean and SE are based on adjusted analyses. Baseline score is the adjusted score.

aerobic exercise for managing depressive symptoms in patients with breast cancer receiving chemotherapy. A minimal important difference for the CES-D has not been identified but our effect size of −0.9 points for the HIGH group translates into a small standardized effect size of −0.19. Although not statistically significant in our study, this effect size is comparable with those reported in systematic reviews of exercise trials that have compared an exercise intervention to usual care (i.e., no exercise). For example, Craft and colleagues (11) reported an effect size for all cancer survivors of $d = -0.22$ and for breast cancer survivors specifically of $d = -0.25$. Brown and colleagues (10) reported an effect size for all cancer survivors of $d = -0.13$ and for breast cancer survivors specifically of $d = -0.17$. Finally, Carayol and colleagues (12) reported an effect size for patients with breast cancer on adjuvant therapy of $d = -0.27$.

Although unlikely to be clinically important even if it was statistically significant, this small effect in the CARE Trial was obtained over and above a standard aerobic exercise program. The comparison of higher dose exercise programs with a standard dose of aerobic exercise provides the most rigorous test of the causal effects of exercise on depressive symptoms because it controls for the benefits of a standard dose of aerobic exercise as well as many nonexercise-related effects that may improve psychosocial functioning such as attention from staff, social interactions with the trainers and other participants, and expectation of benefit. Of course, the exercise interventions in the CARE Trial were not matched exactly for time and, therefore, provided the higher dose exercise interventions more time for social interaction with staff and other participants. Nevertheless, if the small effect of the CARE Trial is added to the small effect reported in trials that compared exercise with no intervention, it is possible that the total effect of the high-dose aerobic exercise intervention in the CARE Trial could be $d = -0.40$, which would be meaningful (26).

As hypothesized, baseline depression level was a significant moderator of the effects of exercise on depressive symptoms in the CARE Trial. There was no effect of higher dose exercise in patients with subclinical levels of depressive symptoms at baseline; however, both the higher dose exercise interventions (HIGH and COMB) produced meaningful standardized effect sizes of $d = -0.40$ to -0.50 compared with STAN in patients who had clinical levels of depressive symptoms at baseline. This finding is consistent with the meta-analysis of Schneider and colleagues (13) showing that baseline depression is a strong predictor of the effectiveness of psychosocial

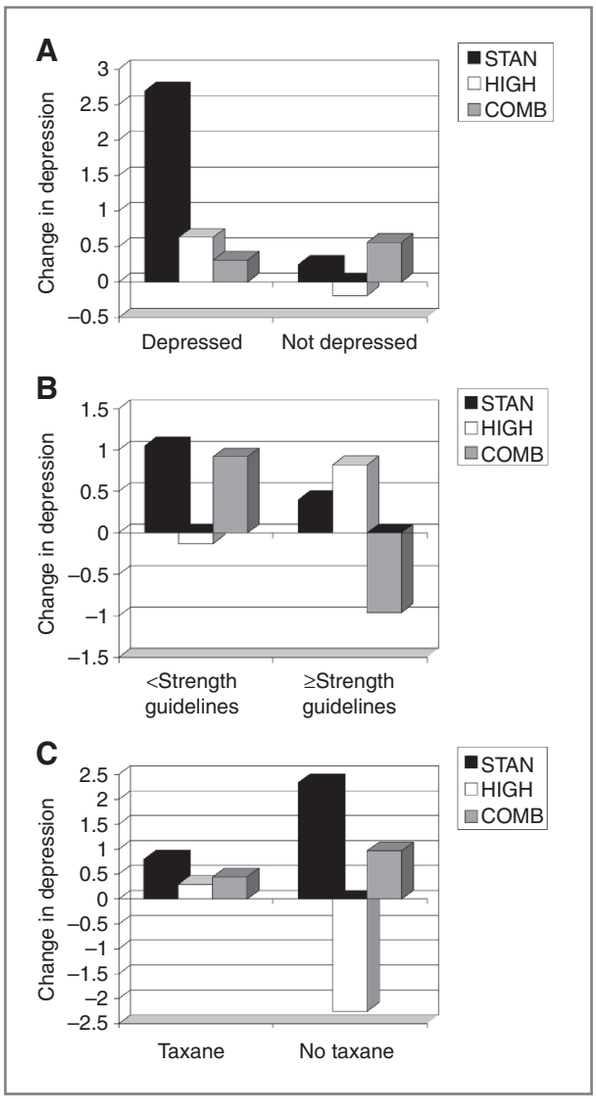

Figure 2. Effects of exercise dose and type on change in depression during breast cancer chemotherapy by baseline depression level (A), baseline strength exercise (B), and chemotherapy regimen (C).

interventions in patients with cancer. It is also consistent with the standardized effect sizes of $d = -0.60$ reported in meta-analyses of exercise interventions in clinically depressed patients without cancer (9, 28). These data suggest that exercise interventions targeted to patients with breast cancer with depression may yield clinically important benefits.

Two other significant interaction effects were identified. The HIGH intervention seemed to be superior for patients who were not receiving taxanes and had no experience with weight training. Conversely, the COMB intervention seemed to be superior for patients who already had experience with weight training. Taken together, these data suggest that COMB programs may be most beneficial for managing depressive symptoms in patients with modest functioning and previous experience with weight training. Conversely, HIGH programs may be most beneficial in patients with good functioning and no experience with weight training. Additional research identifying which patients with cancer respond best to which type of exercise intervention for managing depressive symptoms will inform more targeted interventions.

Several factors may explain the benefits of exercise on depression (28). Biologic explanations include monoamine neurotransmitters, endorphins, anti-inflammatory cytokines, cerebral blood flow, and hypothalamic–pituitary–adrenal axis function (28). Psychosocial explanations include social interaction, distraction, improved self-esteem, behavioral activation, and sense of achievement (28). Given the design of the CARE Trial, the psychosocial explanations are largely controlled. In fact, the finding of higher self-esteem in the STAN group actually works against the biologic effects of the higher dose interventions. Strategies to maintain the self-esteem of patients involved in higher dose exercise interventions may result in larger benefits.

As just noted, paradoxically, STAN was superior to COMB for self-esteem, especially by the end of the intervention (see Fig. 1D). We previously reported that both a standard aerobic exercise and a standard strength exercise program were superior to no exercise for improving self-esteem in patients with breast cancer receiving chemotherapy (29). The observation of a "negative" dose–response effect of exercise on self-esteem is intriguing. One possible explanation is that the more difficult higher dose exercise interventions resulted in objectively poorer adherence that may have led to perceptions of failure and feelings of disappointment. These data suggest that difficult and demanding exercise interventions in patients with breast cancer receiving chemotherapy may lead to lower self-esteem if they cannot be completed successfully. This "adverse effect" of higher dose exercise interventions needs to be balanced with potential gains in symptom management, quality of life, and possibly breast cancer outcomes. Nevertheless, the CARE Trial identifies one of the first "psychosocial adverse effects" of higher dose exercise interventions. Future trials should provide significant support and positive feedback to patients with breast cancer participating in demanding exercise interventions.

Our trial's strengths include being the largest exercise randomized controlled trial to examine psychosocial distress in patients with cancer, the innovative design that examined exercise dose and type effects, multicenter recruitment, supervised exercise, good adherence rates, validated self-report measures of psychosocial distress at multiple time points, intention-to-treat analysis, and trivial loss-to-follow-up. Limitations include the modest recruitment rate, the secondary focus on psychosocial distress, and the slightly lower adherence rates among the higher dose exercise groups that may have partly diluted the hypothesized beneficial effects of the higher dose interventions.

In summary, our analyses of the secondary psychosocial outcomes from the CARE Trial suggest that higher

dose exercise programs do not help manage psychosocial distress in unselected patients with breast cancer during chemotherapy, but may be effective for patients with clinical levels of depressive symptoms at baseline. A phase III exercise trial targeting depressed patients with breast cancer is warranted. Given the benefits of exercise on other outcomes in patients with cancer, higher dose exercise interventions may be an attractive intervention to manage mild to moderate depression. Additional research on the optimal exercise prescription for managing psychosocial distress in various cancer patient groups is needed.

Disclosure of Potential Conflicts of Interest

R.J. Segal is a consultant/advisory board member of Roche, Amgen, and Novartis. No potential conflicts of interest were disclosed by the other authors.

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Grant Support

This work was supported by a grant from the Canadian Breast Cancer Research Alliance (#91807; to K.S. Courneya, D. McKenzie, R.J. Segal, K.A. Gelmon, J. Mackey, R.D. Reid, Y. Yasui, and C.M. Friedenreich). K.S. Courneya and Y. Yasui were supported by the Canada Research Chairs Program. Y. Yasui and C.M. Friedenreich were supported by Health Senior Scholar Awards from Alberta Innovates-Health Solutions. C.M. Friedenreich was also supported by the Alberta Cancer Foundation's Weekend to End Women's Cancers Breast Cancer Chair.

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Received November 11, 2013; revised January 16, 2014; accepted February 19, 2014; published OnlineFirst March 5, 2014.

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