Effects of Exercise during Adjuvant Chemotherapy on Breast Cancer Outcomes

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ABSTRACT

COURNEYA, K. S., R. J. SEGAL, D. C. MCKENZIE, H. DONG, K. GELMON, C. M. FRIEDENREICH, Y. YASUI, R. D. REID, J. J. CRAWFORD, and J. R. MACKEY. Effects of Exercise during Adjuvant Chemotherapy on Breast Cancer Outcomes. *Med. Sci. Sports Exerc.*, Vol. 46, No. 9, pp. 1744–1751, 2014. Observational studies suggest that physical activity after a breast cancer diagnosis is associated with improved cancer outcomes; however, no randomized data are available. Here, we report an exploratory follow-up of cancer outcomes from the Supervised Trial of Aerobic versus Resistance Training (START). **Methods**: The START was a Canadian multicenter trial that randomized 242 breast cancer patients between 2003 and 2005 to usual care (n = 82), supervised aerobic (n = 78), or resistance (n = 82) exercise during chemotherapy. The primary end point for this exploratory analysis was disease-free survival (DFS). Secondary end points were overall survival, distant DFS, and recurrence-free interval. The two exercise arms were combined for analysis (n = 160), and selected subgroups were explored. **Results**: After a median follow-up of 89 months, there were 25/160 (15.6%) DFS events in the exercise groups and 18/82 (22.0%) in the control group. Eight-year DFS was 82.7% for the exercise groups compared with 75.6% for the control group (HR, 0.68; 95% confidence interval (CI), 0.37–1.24; log-rank, P = 0.21). Slightly stronger effects were observed for overall survival (HR, 0.60; 95% CI, 0.27–1.33; log-rank, P = 0.21), distant DFS (HR, 0.62; 95% CI, 0.32–1.19; log-rank, P = 0.15), and recurrence-free interval (HR, 0.58; 95% CI, 0.30–1.11; Gray test, P = 0.095). Subgroup analyses suggested potentially stronger exercise effects on DFS for women who were overweight/obese (HR, 0.59; 95% CI, 0.27–1.27), had stage II/III cancer (HR, 0.61; 95% CI, 0.31–1.20), estrogen receptor-positive tumors (HR, 0.58; 95% CI, 0.26–1.29), human epidermal growth factor receptor 2-positive tumors (HR, 0.21; 95% CI, 0.04–1.02), received taxane-based chemotherapies (HR, 0.46; 95% CI, 0.19–1.15), and ≥85% of their planned chemotherapy (HR, 0.50; 95% CI, 0.25–1.01). **Conclusions**: This exploratory follow-up of the START provides the first randomized data to suggest that adding exercise to standard chemotherapy may improve breast cancer outcomes. A definitive phase III trial is warranted. **Key Words:** PHYSICAL ACTIVITY, DISEASE-FREE SURVIVAL, RANDOMIZED CONTROLLED TRIAL, RECURRENCE, SURVIVAL

Observational studies suggest that physical activity after a breast cancer diagnosis is associated with a lower risk of breast cancer-specific and all-cause mortality (1,15). Some studies also support a dose–response association between physical activity and breast cancer outcomes and suggest possible effect modification by disease stage, body mass index, and estrogen receptor (ER) status (1,15). Several small randomized trials in breast cancer survivors have also provided supportive biomarker data showing that exercise interventions may alter the insulin pathway, inflammation, and cell-mediated immunity in a manner consistent with a lower risk of breast cancer events (1). To date, however, there are no randomized trials examining the effects of exercise on cancer outcomes in any cancer patient group. This article reports an exploratory follow-up of cancer outcomes from the Supervised Trial of Aerobic versus Resistance Training (START).

The START was originally designed to examine the independent effects of aerobic and resistance exercise on quality of life, health-related fitness, and other patient-reported outcomes

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in 242 breast cancer patients receiving adjuvant chemotherapy (8). Several effects that may portend improved cancer outcomes for the exercise groups were observed in the START including improved body fat percentage, lean body mass, cardiovascular fitness, and chemotherapy completion rate (8). Although the START was not originally designed or powered to examine breast cancer outcomes, it provides an opportunity to conduct hypotheses-generating analyses similar to a phase II randomized drug trial (4). Given this exploratory approach, this article reports several efficacy end points and selected subgroup analyses that may inform a possible phase III trial on this question.

METHODS

Setting and participants. Conduct of the START has been described previously (8). Briefly, participants were recruited between February 2003 and July 2005 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 a written informed consent from all participants. Eligibility criteria included English- or French-speaking nonpregnant women ≥18 yr old with stage I–IIIA breast cancer starting adjuvant chemotherapy. Women were excluded if they had incomplete axillary surgery, transabdominal rectus abdominus muscle reconstructive surgery, uncontrolled hypertension, cardiac illness, and psychiatric illness or were otherwise not cleared 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 initiating chemotherapy, and interested participants completed a questionnaire, physical fitness test, and dual-energy x-ray absorptiometry scan before randomization. Participants were stratified by center and chemotherapy regimen (taxane-based vs non–taxane-based) and randomly assigned to either aerobic exercise training (AET), resistance exercise training (RET), or a usual care (UC) control group in a 1:1:1 ratio using a computer-generated randomization 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. AET and RET participants were asked to exercise for the duration of their chemotherapy, including delays, beginning 1–2 wk after starting chemotherapy and ending 3 wk after completing chemotherapy. All exercise sessions were supervised by qualified exercise trainers. Warm-up and cool-down periods were 5 min of light aerobic activity and stretching. The AET group was asked to exercise three times per week on a cycle, treadmill, or elliptical ergometer beginning at 60% of their $\dot{V}O_{2max}$ for weeks 1–6 and progressing to 70% during weeks 7–12 and 80% beyond week 12. Exercise duration began at 15 min for weeks 1–3 and increased by 5 min every 3 wk until 45 min at week 18. The RET group was asked to exercise three times per week, performing two sets of 8–12 repetitions of nine different exercises at 60%–70% of their estimated 1-repetition maximum. Resistance was increased by 10% when participants completed >12 repetitions. Exercise adherence was tracked by the exercise trainers, and any missed exercise sessions could be made-up within the same week. The UC control group was asked not to initiate an exercise program during chemotherapy but was offered a 1-month exercise crossover after postintervention assessments.

Definition of primary and secondary efficacy end points. Efficacy end points were defined on the basis of the Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (the STEEP system) (14). For this exploratory analysis, disease-free survival (DFS) was selected as the primary end point because it is the most common end point in breast cancer adjuvant trials. DFS was defined as the time from randomization to documentation of the first of any of the following events: invasive ipsilateral breast tumor recurrence; local, regional, or distant recurrence; invasive contralateral breast cancer; ipsilateral and contralateral ductal carcinoma *in situ* (DCIS), second primary invasive cancer (excluding carcinoma *in situ* and skin cancer other than melanoma); or death from any cause. Secondary end points were overall survival (OS), distant DFS (DDFS), and recurrence-free interval (RFI). OS was defined as time from randomization to death from any cause. DDFS was selected because it consists of events that are either lethal (death from any cause) or a direct threat to patient survival (distant recurrence or second primary invasive cancer). RFI was selected because it consists of events directly attributable to the original breast cancer including invasive ipsilateral breast tumor recurrence; local, regional, or distant recurrence; and death from breast cancer. Efficacy end points restricted to breast cancer events are common in lifestyle trials (6,22,23,25).

Collection of study end points. Study end points were obtained retrospectively. Between June and August 2012, each cancer center completed an electronic medical chart abstraction using a standardized form and coding system previously developed and tested (11). Data abstracted included relapse, date of relapse, nature of relapse (DCIS, local, regional, or distant), site of first metastasis (if distant), second primary cancer, date of second primary cancer, site of second primary cancer, DCIS or invasive (if breast cancer), death, date of death, cause of death, and treatment received after adjuvant chemotherapy (radiation, endocrine therapy, and trastuzumab). Any ambiguities were reviewed by the medical oncology investigators. Date of last known follow-up was also recorded. Follow-up time was censored at the time of death or the last documented contact date.

Disease and treatment data. Disease and treatment data were collected prospectively from medical chart reviews as part of the original START protocol using standardized chart abstraction procedures. Data included tumor size, grade,

histology, nodal status, clinical stage, ER and progesterone receptor status, human epidermal growth factor receptor-2 (HER2) status, extent of surgery, chemotherapy regimen, and average relative dose intensity (RDI) of the originally planned chemotherapy regimen.

Statistical analyses. Statistical analyses were conducted in 2013. The Kaplan–Meier product-limit method was used to describe survival probabilities for DFS, OS, and DDFS outcomes and provide their estimates at 8-yr postrandomization. Log-rank tests were used to assess differences in the (unadjusted) survival probabilities by arm. For RFI, cumulative incidence curves were used because non-breast cancer deaths are competing-risk events. The Gray test was used to assess differences in the (unadjusted) cumulative incidence curve by arm. A Cox proportional hazards model was used to estimate HR and 95% confidence intervals (CI) for DFS, OS, and DDFS. The primary analyses were unadjusted. Secondary analyses were also conducted, consisting of a "stratified-adjusted" model that adjusted for the two stratification variables of center (Edmonton vs Ottawa vs Vancouver) and chemotherapy regimen (non-taxane vs taxane) and a "fully adjusted" model that adjusted for the same two stratification variables plus several key prognostic variables that have been adjusted for in the large nutrition trials, as follows (6,22): ER status (positive vs negative), tumor size (≤2 cm vs >2–5 cm vs >5 cm), nodal status (negative vs 1–3 positive nodes vs ≥4 positive

TABLE 1. Baseline demographic and medical characteristics in the START, overall and by group assignment.

				Separate Exercise Arms	
	Total (n = 242)	UC (n = 82)	Exercise (n = 160)	RET (n = 82)	AET (n = 78)
Variable	n (%)	n (%)	n (%)	n (%)	n (%)
Age at random assignment					
<50 yr	132 (54.5)	42 (51.2)	90 (56.2)	43 (52.4)	47 (60.3)
≥50 yr	110 (45.5)	40 (48.8)	70 (43.8)	39 (47.6)	31 (39.7)
Body mass index					
Normal weight (<25 kg·m^{-2})	110 (45.5)	32 (39.0)	78 (48.8)	45 (54.9)	33 (42.3)
Overweight (25–29.9 kg·m^{-2})	82 (33.9)	31 (37.8)	51 (31.9)	23 (28.0)	28 (35.9)
Obese (≥30 kg·m^{-2})	50 (20.7)	19 (23.2)	31 (19.4)	14 (17.1)	17 (21.8)
Disease stage					
I	60 (24.8)	20 (24.4)	40 (25.0)	22 (26.8)	18 (23.1)
IIa	99 (40.9)	30 (36.6)	69 (43.1)	36 (43.9)	33 (42.3)
IIb	48 (19.8)	22 (26.8)	26 (16.2)	9 (11.0)	17 (21.8)
IIIa	35 (14.5)	10 (12.2)	25 (15.6)	15 (18.3)	10 (12.8)
Primary tumor size					
≤2 cm	122 (50.4)	37 (45.1)	85 (53.1)	48 (58.5)	37 (47.4)
>2–5 cm	106 (43.8)	41 (50.0)	65 (40.6)	28 (34.1)	37 (47.4)
>5 cm	14 (5.8)	4 (4.9)	10 (6.2)	6 (7.3)	4 (5.1)
Nodal status					
Negative	108 (44.6)	38 (46.3)	70 (43.8)	37 (45.1)	33 (42.3)
1–3 positive nodes	109 (45.0)	36 (43.9)	73 (45.6)	34 (41.5)	39 (50.0)
≥4 positive nodes	25 (10.4)	8 (9.8)	17 (10.6)	11 (13.4)	6 (7.7)
Tumor grade					
1	24 (9.9)	4 (4.9)	20 (12.5)	9 (11.0)	11 (14.1)
2	86 (35.5)	30 (36.6)	56 (35.0)	31 (37.8)	25 (32.1)
3	132 (54.5)	48 (58.5)	84 (52.5)	42 (51.2)	41 (53.8)
ER status					
Negative	71 (29.3)	36 (43.9)	35 (21.9)	20 (24.4)	15 (19.2)
Positive	171 (70.7)	46 (56.1)	125 (78.1)	62 (75.6)	63 (80.8)
Progesterone receptor status					
Negative	83 (34.3)	39 (47.6)	44 (27.5)	26 (31.7)	18 (23.1)
Positive	126 (52.1)	33 (40.2)	93 (58.1)	41 (50.0)	52 (66.7)
Unknown	33 (13.6)	10 (12.2)	23 (14.4)	15 (18.3)	8 (10.3)
Intrinsic subtype					
Luminal/HER2 negative	150 (62.0)	38 (46.3)	112 (70.0)	57 (69.5)	55 (70.5)
HER2 positive	30 (12.4)	14 (17.1)	16 (10.0)	6 (7.3)	10 (12.8)
Triple negative	62 (25.6)	30 (36.6)	32 (20.0)	19 (23.2)	13 (16.7)
Extent of surgery					
Breast sparing	143 (59.1)	49 (59.8)	94 (58.8)	50 (61.0)	44 (56.4)
Mastectomy	99 (40.9)	33 (40.2)	66 (41.2)	32 (39.0)	34 (43.6)
Chemotherapy regimen					
Non-taxane	167 (69.0)	54 (65.9)	113 (70.6)	58 (70.7)	55 (70.5)
Taxane	75 (31.0)	28 (34.1)	47 (29.4)	24 (29.3)	23 (29.5)
Average RDI					
<85%	66 (27.3)	28 (34.1)	38 (23.8)	18 (22.0)	20 (25.6)
≥85%	176 (72.7)	54 (65.9)	122 (76.2)	64 (78.0)	58 (74.4)
Adjuvant radiation therapy					
No	38 (15.7)	14 (17.1)	24 (15.0)	8 (9.8)	16 (20.5)
Yes	204 (84.3)	68 (82.9)	136 (85.0)	74 (90.2)	62 (79.5)
Adjuvant endocrine therapy					
No	73 (30.2)	36 (43.9)	37 (23.1)	20 (24.4)	17 (21.8)
Yes	169 (69.8)	45 (56.1)	123 (76.9)	62 (75.6)	61 (78.2)
Adjuvant Herceptin					
No	212 (87.6)	68 (82.9)	144 (90.0)	76 (92.7)	68 (87.2)
Yes	30 (12.4)	14 (17.1)	16 (10.0)	6 (7.3)	10 (12.8)

nodes), extent of surgery (breast sparing vs mastectomy), and age (<50 yr vs ≥50 yr).

For DFS and RFI, subgroup analyses were conducted on the basis of biological plausibility and epidemiological data suggesting potentially different associations between exercise and cancer outcomes in some subgroups (1,15). The subgroups compared were age at randomization (<50 yr vs ≥50 yr), body mass index (normal weight (<25 $kg \cdot m^{-2}$) vs overweight/obese (≥25 $kg \cdot m^{-2}$)), disease stage (I vs II/III), ER status (negative vs positive), intrinsic subtype (luminal/HER2 vs HER2 positive vs triple negative), chemotherapy regimen (non-taxane vs taxane), and RDI of the originally planned chemotherapy regimen (<85% vs ≥85%). The exercise arms were combined for analyses to increase study power because there was no *a priori* reason to expect differential effects of aerobic or resistance exercise on cancer outcomes. Nevertheless, descriptive event data are reported separately for the two exercise arms. For all analyses, the intention-to-treat principle was used. All *P* values are two-sided, and all analyses were conducted with SPSS version 20.

RESULTS

Flow of participants through the trial has been reported previously (8). Briefly, 242 of 736 eligible participants (33%) were recruited and 82 were randomized to control, 82 to RET, and 78 to AET (160 to the exercise arms combined). Baseline characteristics are reported in Table 1. The AET and RET groups attended 72.0% and 68.2% of their supervised exercise sessions, respectively. At postintervention, 25 of 82 participants (30.5%) in the control group opted for the 1-month supervised exercise crossover. Of 201 participants (83%) providing 6-month follow-up data, there were no group differences in reports of weekly aerobic exercise minutes ($P = 0.86$), with the control group reporting 150 (SD, 197), the AET group reporting 138 (SD, 144), and the RET group reporting 152 (SD, 166). Strength training was slightly more frequent in the RET group with 1.1 session per week (SD, 1.3) compared with 0.8 (SD, 1.1) in the control group and 0.6 (SD, 1.3) in the AET group ($P = 0.084$).

Efficacy end points. The median interval between last known contact and the analysis end date was 4.0 months for both the exercise and control groups. After a median follow-up of 89 months (interquartile range, 81–96) in surviving patients, there were 43 DFS events, 24 OS events, 36 DDFS events, and 37 RFI events (Table 2). There were 25 (15.6%) DFS events in the exercise groups and 18 (22.0%) in the control group (log-rank, $P = 0.21$). Eight-year DFS was 82.7% for the exercise groups compared with 75.6% for the control group (HR, 0.68; 95% CI, 0.37–1.24) (Fig. 1A). There were 13 deaths (8.1%) in the exercise groups and 11 (13.4%) in the control group (log-rank, $P = 0.21$). Eight-year OS was 91.2% in the exercise groups compared with 82.7% in the control group (HR, 0.60; 95% CI, 0.27–1.33) (Fig. 1B). There were 20 DDFS events (12.5%) in the exercise groups and 16 (19.5%) in the control group (log-rank, $P = 0.15$). Eight-year DDFS was 86.7% in the exercise groups compared with 78.3% in the control group (HR, 0.62; 95% CI, 0.32–1.19; Fig. 1C). Finally, there were 20 RFI events (12.5%) in the exercise groups and 17 (20.7%) in the control group (Gray, $P = 0.095$). Eight-year cumulative incidence of RFI was 12.6% in the exercise groups compared with 21.6% in the control group (HR, 0.58; 95% CI, 0.30–1.11) (Fig. 1D). Adjusted HR are reported in Table 3, with the fully-adjusted model showing some attenuation for DFS, OS, and DDFS but not RFI.

Subgroup analyses for DFS and RFI are reported in Figures 2A and 2B, respectively. There was a suggestion that exercise had stronger effects on DFS and RFI in women who were overweight/obese, had stage II/III cancer, ER-positive tumors, and HER2 positive tumors, and received

TABLE 2. Observed events in the START, overall and by group assignment.

				Separate Exercise Arms	
	Total (*n* = 242)	Control (*n* = 82)	Exercise (*n* = 160)	RET (*n* = 82)	AET (*n* = 78)
Event	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Invasive ipsilateral breast tumor recurrence	2 (0.8)	0 (0.0)	2 (1.3)	2 (2.4)	0 (0.0)
Local/regional invasive recurrence	8 (3.3)	4 (4.9)	4 (2.5)	3 (3.7)	1 (1.3)
Distant recurrence	28 (11.6)	13 (15.9)	15 (9.4)	6 (7.3)	9 (11.5)
Site of first metastasis[a]					
Bone	16 (6.6)	5 (6.1)	11 (6.9)	3 (3.7)	8 (10.3)
Liver	12 (5.0)	4 (4.9)	8 (5.0)	2 (2.4)	6 (7.7)
Lung	7 (2.9)	3 (3.7)	4 (2.5)	1 (1.2)	3 (3.8)
Brain	2 (0.8)	1 (1.2)	1 (0.6)	1 (1.2)	0 (0.0)
Nodes	2 (0.8)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (0.8)	1 (1.2)	1 (0.6)	1 (1.2)	0 (0.0)
Breast cancer death	22 (9.1)	10 (12.2)	12 (7.5)	6 (7.3)	6 (7.7)
Non-breast cancer death	2 (0.8)	1 (1.2)	1 (0.6)	1 (1.2)	0 (0.0)
Invasive contralateral breast cancer	2 (0.8)	0 (0.0)	2 (1.3)	0 (0.0)	2 (2.6)
Second primary invasive cancer (non-breast)	4 (1.7)	2 (2.4)	2 (1.3)	2 (2.4)	0 (0.0)
Melanoma	2 (0.8)	1 (1.2)	1 (0.6)	1 (1.2)	0 (0.0)
Tongue	1 (0.4)	0 (0.0)	1 (0.6)	1 (1.2)	0 (0.0)
Thyroid	1 (0.4)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
DFS events	43 (17.8)	18 (22.0)	25 (15.6)	13 (15.9)	12 (15.4)
RFI events	37 (15.3)	17 (20.7)	20 (12.5)	10 (12.2)	10 (12.8)
DDFS events	36 (14.9)	16 (19.5)	20 (12.5)	11 (13.4)	9 (11.5)
OS events	24 (9.9)	11 (13.4)	13 (8.1)	7 (8.5)	6 (7.7)

[a]Site of first metastasis may include more than one site.

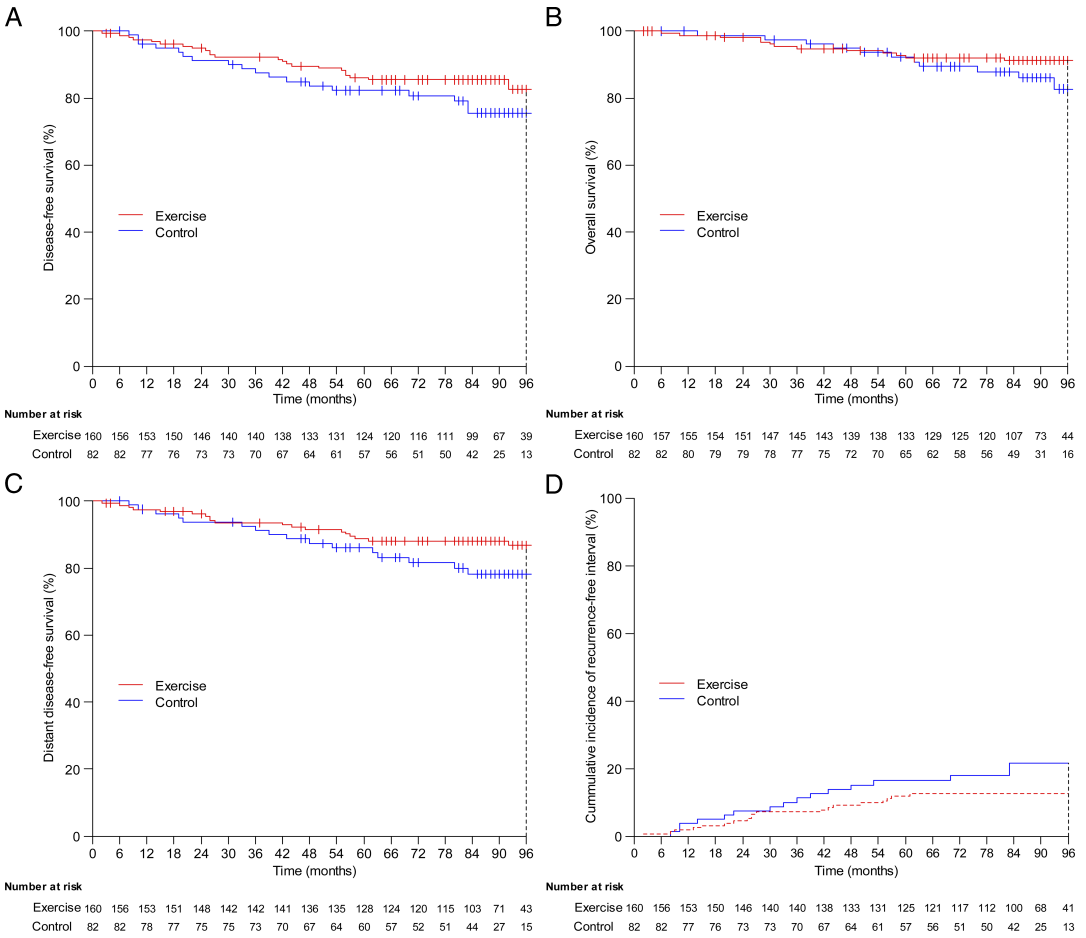

FIGURE 1—DFS (A), OS (B), DDFS (C), and RFI (D) by randomized group assignment.

taxane-based chemotherapies and optimal chemotherapy dosing. The most notable subgroup effect was for patients who received optimal chemotherapy dosing (defined as having received 85% or more of the intended RDI), with a borderline significant effect for DFS (HR, 0.50; 95% CI, 0.25–1.01) and a significant effect for RFI (HR, 0.38; 95% CI, 0.18–0.81).

DISCUSSION

To our knowledge, there are no randomized controlled trials demonstrating that exercising after a cancer diagnosis can alter the course of the disease or extend survival. In this exploratory follow-up of the START, there was a suggestion that exercise during adjuvant chemotherapy may improve several efficacy end points, although none of the effects achieved statistical significance. Nevertheless, the magnitude of the effects seem to be meaningful, with absolute 8-yr survival differences between 7% and 9% and relative rate reductions between 30% and 40% for the unadjusted analyses and 25% to 40% for the adjusted analyses. The strongest effect was for RFI events, which are directly related to the original breast cancer. This effect was not attenuated in the adjusted analyses. In exploratory subgroup analyses, the strongest effects were in women who were overweight/obese, had stage II/III cancers, ER-positive tumors, and HER2-positive tumors, and received taxane-based chemotherapies and optimal chemotherapy dosing.

TABLE 3. Efficacy end points by group assignment.

	Total (n = 242)	Control (n = 82)	Exercise (n = 160)			
End point	n (%)	n (%)	n (%)	Unadjusted HR (95% CI)	Stratification Adjusted[a] HR (95% CI)	Fully Adjusted[b] HR (95% CI)
DFS	43 (17.8)	18 (22.0)	25 (15.6)	0.68 (0.37–1.24)	0.69 (0.38–1.27)	0.76 (0.40–1.43)
OS	24 (9.9)	11 (13.4)	13 (8.1)	0.60 (0.27–1.33)	0.62 (0.28–1.39)	0.72 (0.31–1.67)
RFI	37 (15.3)	17 (20.7)	20 (12.5)	0.58 (0.30–1.11)	0.60 (0.31–1.15)	0.61 (0.31–1.21)
DDFS	36 (14.9)	16 (19.5)	20 (12.5)	0.62 (0.32–1.19)	0.64 (0.33–1.24)	0.72 (0.36–1.42)

[a]Adjusted for the two stratification variables of center (Edmonton vs Ottawa vs Vancouver) and chemotherapy regimen (taxane vs non-taxane).
[b]Adjusted for the two stratification variables plus ER status (positive vs negative), tumor size (≤2 cm vs >2–5 cm vs >5 cm), nodal status (negative vs 1–3 positive nodes vs ≥4 positive nodes), extent of surgery (breast sparing vs mastectomy), and age (<50 yr vs ≥50 yr).

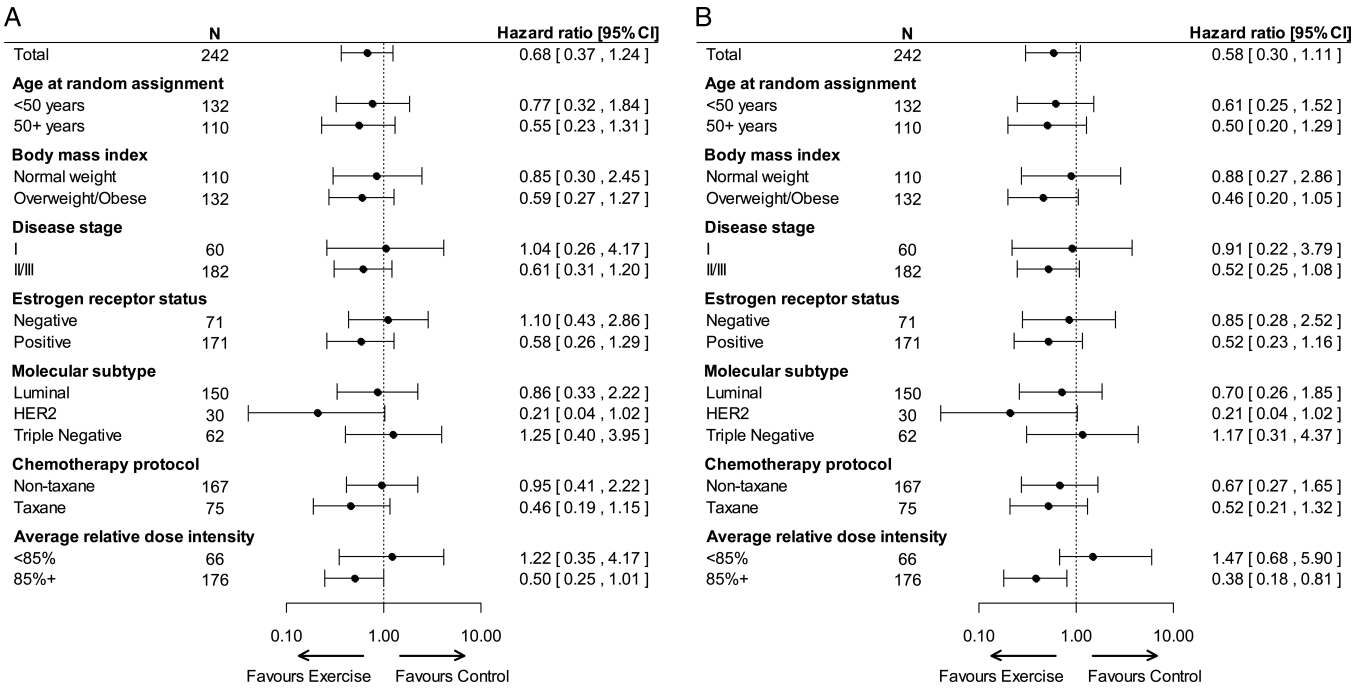

FIGURE 2—Subgroup analyses of DFS (A) and RFI (B).

There are no randomized exercise trials examining cancer outcomes in cancer patients with which to compare our results. There are two large nutrition trials in breast cancer patients that inform how lifestyle changes may affect breast cancer outcomes (6,22). The Women's Intervention Nutrition Study (WINS) (6) randomized 2437 postmenopausal breast cancer patients to a dietary fat reduction intervention or usual diet and found that patients on the reduced-fat diet had improved relapse-free survival (HR, 0.76; 95% CI, 0.60–0.98). In subgroup analyses, the effect was largely confined to women with ER-negative tumors (HR, 0.58; 95% CI, 0.37–0.91). The Women's Healthy Eating and Living (WHEL) trial (22) randomized over 3000 breast cancer patients to a diet that was high in vegetables, fruit, and fiber and low in fat versus usual diet and found no effects on breast cancer outcomes. The most common explanation for the disparate results between the two trials is that the WINS intervention produced a modest weight loss whereas the WHEL intervention did not. Neither trial intervened on physical activity.

To our knowledge, there are three large ongoing lifestyle trials in cancer survivors with cancer outcomes as end points (7,23,25). The Diet and Androgens-5 trial (25) is examining the effects of a combined Mediterranean diet and exercise intervention versus general lifestyle recommendations in 1200 early-stage breast cancer survivors within 5 yr of their diagnosis. The Exercise and Nutrition to Enhance Recovery and Good Health for You trial (23) is a vanguard trial examining the effects of an intensive weight loss intervention versus standard weight loss in 693 overweight or obese early-stage breast cancer survivors within 5 yr of diagnosis, with the potential to expand to 2500 in the full trial. Finally, the Colon Health and Life-Long Exercise Change trial (7) is examining the effects of a 3-yr exercise intervention on DFS in 962 high-risk stage II or III colon cancer survivors who completed chemotherapy within the past 2–6 months. None of these trials are examining the effects of exercise on breast cancer outcomes, and none of them begin the lifestyle intervention during adjuvant treatment.

There are several possible explanations why exercise during adjuvant breast cancer chemotherapy may improve cancer outcomes. One possibility is that exercise improves 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 at approximately 85% (2,3,26). It was previously reported that the exercise groups in the START completed a slightly higher RDI than that in the control group (8). It is unclear, however, if the observed RDI differences of 3%–6% could translate into improved disease outcomes. Moreover, the strongest and most reliable effect for exercise was in patients who received at least 85% of their planned RDI, suggesting that exercise may be most effective in patients who receive optimal chemotherapy dosing.

A second possible explanation is that exercise may potentiate the effects of cytotoxic chemotherapy through influences on drug distribution, pharmacodynamics, and metabolism. Animal and clinical studies suggest potential interactions between exercise and anticancer effects of cytotoxic chemotherapy mediated by changes in nitric oxide–mediated peripheral blood flow (12,13), angiogenesis (18), endogenous antioxidant expression (17), and drug pharmacokinetics (24). A third possible explanation is that exercise provides an additive benefit beyond current chemotherapy

drugs mediated by mechanisms unrelated to interaction effects. Exercise has been shown to reduce markers of systemic inflammation (9), modulate the insulin pathway (1), favorably affect cell-mediated immunity (10), and change steroid hormone levels (19), although its effects during chemotherapy have not been studied in humans.

It is also possible that the exercise groups were more likely to exercise into survivorship and, therefore, achieve sustained biomarker changes over the course of many years that are unrelated to any interactions with adjuvant chemotherapy. The 6-month follow-up of exercise behavior does not support this explanation, with all three groups reporting roughly the same volume of aerobic and resistance exercise. Of course, the follow-up was short-term, relied on self-report, and included a 1-month exercise crossover for approximately 30% of the control group, so this explanation cannot be ruled out entirely.

Other explanations relate to changes in health-related fitness that were documented in the START and may be linked to disease outcomes. In the START, AET blunted a decline in maximal oxygen consumption in the UC group of about 2.0 $mL \cdot mg^{-1} \cdot kg^{-1}$ or 8% (8). Aerobic fitness is an established predictor of disease and mortality in other populations (21). RET increased muscular strength by 25%–35% (8). Muscular strength is associated with lower mortality in other populations (20). Finally, 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 (5), with most explanations focusing on adiposity rather than body weight (16).

An exercise intervention during chemotherapy is best viewed as an adjuvant treatment trial rather than a survivorship trial. Most lifestyle trials have initiated the intervention in the survivorship phase including the WINS (6) and WHEL trials (22) and the ongoing Colon Health and Life-Long Exercise Change (7), Diet and Androgens-5 trial (25), and Exercise and Nutrition to Enhance Recovery and Good Health for You trial (23). The optimal timing of lifestyle interventions with cancer outcomes is unclear. The potential advantages of lifestyle interventions during treatment are the shorter intervention period and the possibility of capitalizing on treatment interactions. Disadvantages may include recruitment and adherence challenges due to the side effects of treatments. The potential advantages of lifestyle interventions during survivorship may be better recruitment and adherence rates and a longer intervention period to alter disease outcomes. This longer intervention period, however, may also create challenges in terms of longer-term adherence and costs.

To our knowledge, the START provides the first randomized data comparing exercise with control for cancer outcomes in any cancer patient group. The strengths of conducting these exploratory analyses in the START are the well-defined patient population of incident breast cancer cases initiating adjuvant chemotherapy, the breadth and quality of the disease and treatment-related data that are superior to other exercise trials and comparable with drug trials, the supervised exercise with good adherence, the 7.5-yr median follow-up, and the biological plausibility of the overall and subgroup findings. Limitations include the 33% recruitment rate, the exploratory nature of the analysis, and the limited follow-up of exercise and fitness outcomes. Moreover, the exercise adherence rate was acceptable but not optimal, suggesting the possibility that improved adherence may produce even stronger effects on cancer outcomes.

Another important limitation is the modest sample size, which is clearly underpowered for any definitive conclusions. Although the point estimates for the exercise effects were promising, the CI were wide and do not even rule out the possibility of an adverse effect of exercise on cancer outcomes. Moreover, the modest sample size did not allow us to examine the outcomes separately for AET and RET. Although the event rates were similar for the AET and RET groups, there are certainly differences in AET and RET that may have implications for cancer outcomes. Despite these limitations, the goal of randomized phase II trials is not to obtain definitive efficacy information but to identify promising experimental regimens that have a high likelihood of success in the phase III setting (4). In our view, this exploratory follow-up of the START for breast cancer outcomes provides further support for a definitive phase III trial on this question.

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