Original Investigation

Effects of a High vs Moderate Volume of Aerobic Exercise on Adiposity Outcomes in Postmenopausal Women
A Randomized Clinical Trial

Christine M. Friedenreich, PhD; Heather K. Neilson, MSc; Rachel O'Reilly, MSc; Aalo Duha, MD; Yutaka Yasui, PhD; Andria R. Morielli, BSc; Scott C. Adams, MSc; Kerry S. Courneya, PhD

Invited Commentary page 776

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IMPORTANCE Body fat increases postmenopausal breast cancer risk. Physical activity may decrease risk through adiposity changes, but the optimal dose of activity is unknown.

OBJECTIVE To compare the effects of 300 vs 150 min/wk of moderate to vigorous aerobic exercise on body fat in postmenopausal women.

DESIGN, SETTING, AND PARTICIPANTS The Breast Cancer and Exercise Trial in Alberta was a 12-month, 2-armed, 2-center randomized dose-comparison trial conducted from June 2010 through June 2013. Participants were 400 inactive postmenopausal women with body mass index 22 to 40, disease-free, nonsmokers, and nonusers of exogenous hormones.

INTERVENTIONS Five d/wk of aerobic exercise (3 d/wk supervised, 2 d/wk unsupervised) for 30 min/session (moderate-volume) or 60 min/session (high volume) achieving 65% to 75% of heart rate reserve for at least 50% of each session. Participants were asked not to change usual diet.

MAIN OUTCOMES AND MEASURES Total body fat, measured from dual energy x-ray absorptiometry scans, was the primary outcome. Other measures included subcutaneous and intra-abdominal fat from computed tomography scans, weight, and waist and hip circumferences.

RESULTS Of 400 women, 384 provided baseline and follow-up adiposity measurements. Median (interquartile range) adherence at full prescription for the high- and moderate-volume groups was 254 (166-290) and 137 (111-150) min/wk, respectively. Mean reductions in total fat were significantly larger in the high- vs moderate-volume group (least-squares mean difference, −1.0% [95% CI, −1.6% to −0.4%], $P = .002$). Subcutaneous abdominal fat and waist to hip ratio decreased significantly more in the high-volume group (least-squares mean difference, −10.8 [95% CI, −19.5 to −2.2] cm^2, $P = .01$, and −0.01 [95% CI, −0.02 to 0.00], $P = .04$, respectively). Changes in weight and intra-abdominal fat were not significantly different between groups (least-squares mean difference, −0.7 [95% CI, −1.6 to 0.2] kg, $P = .11$, and −1.5 [95% CI, −5.9 to 2.9] cm^2, $P = .50$, respectively). Some dose-response effects were stronger for obese women.

CONCLUSIONS AND RELEVANCE In previously inactive postmenopausal women, a 1-year prescription of moderate to vigorous exercise for 300 min/wk was superior to 150 min/wk for reducing total fat and other adiposity measures, especially in obese women. These results suggest additional benefit of higher-volume aerobic exercise for adiposity outcomes and possibly a lower risk of postmenopausal breast cancer.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Christine M. Friedenreich, PhD, Department of Cancer Epidemiology and Prevention Research, CancerControl Alberta, Alberta Health Services, Holy Cross Centre, Room 514, PO Box ACB, 2210 Second St SW, Calgary, AB T2S 3C3, Canada (christine.friedenreich@albertahealthservices.ca).

Physical activity is an inexpensive, noninvasive strategy for disease prevention advocated by public health agencies in North America[1,2] and internationally[3] with recommendations to be physically active at least 150 min/wk at moderate intensity, or 60 to 75 min/wk at vigorous intensity, for overall health. An established benefit of physical activity is body weight regulation. Consensus exists that physical activity is effective for preventing weight gain[4-7] and that generally, sustained physical activity for more than 150 min/wk produces modest weight loss of 2 to 3 kg for overweight and obese adults,[4,8,9] with higher volumes (eg, 225 to 420 min/wk[10]) resulting in greater weight loss.[11,12]

Postmenopausal women may derive unique benefit from exercise because there is a tendency for total[13-15] and abdominal[16] weight gain after menopause; moreover, body fat, abdominal fat, and adult weight gain increase the risk of postmenopausal breast cancer.[17-21] Endometrial and colon cancers, the metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease are also mediated through postmenopausal adiposity.[22] Physical activity decreases postmenopausal breast cancer risk[17,18] partly by regulating body fat.[23] It is unknown, however, to what extent higher exercise volumes influence postmenopausal body fat.

The dose-response benefits of exercise can be estimated most accurately from well-powered randomized clinical trials (RCTs). However, few RCTs with adiposity outcomes have been designed to compare exercise durations,[10,24-33] and, to our knowledge, none have prescribed moderate to vigorous exercise for more than 250 min/wk exclusively to postmenopausal women. Dose-comparison trials have often been shorter than 6 months,[24,27,31,34] included men[10,24,29,31-33] or 50 or fewer participants per arm,[10,24,25,27,28,30-32,34] prescribed lower exercise duration or intensity,[26,32,35] and/or did not measure visceral fat.[10,24,25,27,29-31,34,35] Previously in the Alberta Physical Activity and Breast Cancer Prevention (ALPHA) trial, we randomized 320 postmenopausal women to 225 min/wk moderate to vigorous aerobic exercise or usual inactivity for a period of 12 months and showed that body weight, total fat, and intra-abdominal and subcutaneous abdominal fat decreased significantly vs controls. In exploratory analyses, favorable dose-response trends were found between mean body fat reduction and exercise adherence of less than 150, 150 to 225, and more than 225 min/wk.[36] However, the ALPHA Trial was not designed to examine dose-response effects. In the Breast Cancer and Exercise Trial in Alberta (BETA), we tested whether greater adiposity changes occur in inactive, postmenopausal women randomized to a high-volume (300 min/wk) vs moderate-volume (150 min/wk) exercise prescription. The goal was to inform physical activity guidelines for weight control and the primary prevention of postmenopausal breast cancer.

At a Glance

- We compared adiposity changes in 400 inactive postmenopausal women randomized to 1 year of high-volume (300 min/wk) or moderate-volume (150 min/wk) exercise.
- Mean exercise minutes per week in the moderate-volume and high-volume groups, respectively, were 91% and 85% of prescribed.
- Mean exercise duration was less than 150 min/wk for 22.5% of women in the high-volume group.
- Mean reductions in total body fat, subcutaneous abdominal fat, BMI, and waist to hip ratio were significantly greater ($P < .05$) for women prescribed 300 min/wk aerobic exercise.
- Benefits associated with the 300-min/wk prescription were enhanced for obese women (BMI ≥ 30) with respect to weight, BMI, waist and hip circumference, and subcutaneous abdominal fat.

Methods

The Breast Cancer and Exercise Trial in Alberta was a 2-center, 2-armed RCT conducted in Calgary and Edmonton, Alberta, Canada. Details of the study design and methods were previously published.[37]

Participants

Eligible women were postmenopausal, aged 50 to 74 years, had a body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of 22 to 40, were inactive[37] (≤120 min/wk or no more than 3 d/wk moderate-intensity recreational activity less than 30 minutes/session; baseline estimated maximum oxygen consumption [$\dot{V}O_{2max}$] no more than 34.5 mL/kg/min or, if estimated $\dot{V}O_{2max}$ was 34.6-37.0 mL/kg/min, 7-day accelerometer count less than 10 000 steps/d), and had no previous cancer diagnosis except nonmelanoma skin cancer and no major comorbid condition or recent reconstructive surgery. Women could maintain acceptable heart and lung function in a submaximal treadmill test, were nonusers of exogenous hormones or drugs affecting estrogen metabolism, nonsmokers, consumed no more than 2 drinks of alcohol/d, English speaking, not intending to be away longer than 4 weeks consecutively (8 weeks total) during the intervention, and not participating in or planning a weight loss program. The study protocol (see Supplement 1) was approved by the Alberta Cancer Research Ethics Committee and the Conjoint Health Research Ethics Board of the University of Calgary, and the Health Research Ethics Board of the University of Alberta. All participants provided written informed consent.

Randomization and Blinding

Women were randomly allocated 1:1 to aerobic exercise for 150 or 300 min/wk. Randomization was stratified by study center and baseline BMI using block sizes of 4 or 6 within strata. The random allocation sequence was generated using R software (version 2.11)[38] and user-defined functions. Allocations were concealed in numbered envelopes prepared by staff unrelated to the study team. Study coordinators in Calgary and Edmonton enrolled participants and assigned them to an intervention. Staff were blinded to randomization group during anthropometric measurements and full-body dual-energy x-ray absorptiometry (DXA) scans. The study radiologist (A.D.) was blinded to randomization group when reviewing computed tomographic scans.

Intervention

Exercise volume was increased gradually over a 12-week ramp-up period.[37] The goal by week 13 was to attain 5 d/wk aerobic exercise for 30 minutes (moderate volume) or 60 minutes (high volume) per session, achieving 65% to 75% maximum heart rate reserve for at least half of each workout (fitness levels were reassessed every 3 months). Women received Polar FT4 heart rate monitors (Polar Electro) to use in each supervised or unsupervised session. From weeks 13 through 52, women were prescribed supervised sessions 3 d/wk (Westside Recreation Centre, Calgary, or the Behavioral Medicine Fitness Centre, University of Alberta, Edmonton) and unsupervised home-based exercise 2 d/wk. Weekly exercise logs were used to document activity types, total exercise duration, exercise duration at 65% to 75% of maximum heart rate reserve, mean heart rate, and Borg Ratings of Perceived Exertion.[39] Exercise frequency, duration, and mean heart rate were determined from heart rate monitors and recorded by exercise trainers; participants reported types of activity and Borg Ratings. Participants were instructed not to change usual diet.

Any aerobic activity that raised heart rate to 65% to 75% of heart rate reserve was permitted during the trial. In the first 2 sessions, each participant met one on one with a study exercise trainer who provided orientation to the training facility and a variety of aerobic equipment including treadmills, stationary bicycles, and elliptical trainers. Trainers also provided a comprehensive exercise educational guide[37] developed for BETA that included home-based exercise examples and proper exercise technique instructions for specific activities.

Baseline and Follow-up Measures

A number of variables were assessed for descriptive purposes and to assess possible confounding or effect modification. Demographic information, including race/ethnicity, and medical history was obtained by self-completed questionnaire at baseline and 12-month follow-up. In addition, participants completed the Past Year Total Physical Activity Questionnaire capturing the frequency, duration, and intensity of all occupational, household, recreational, and walking or bicycling to work activities,[40] as well as the Canadian adaptation of the US National Cancer Institute's past-year Diet History Questionnaire.[41] Metabolic equivalent (MET) values were assigned to each activity using the Compendium of Physical Activities[42-44] to derive MET-hours per week for each activity domain. Caloric and nutrient intakes were estimated using Diet*Calc.[45]

At baseline and 12 months, submaximal cardiorespiratory tests were conducted using a multistage, modified Balke treadmill protocol[46]; $\dot{V}O_{2max}$ was estimated as previously described.[37] At the time of fitness testing, standing height and weight were measured by research staff using a balance beam scale and stadiometer. Measures were taken in duplicate (if discrepant, a third measure was taken) and then averaged. Waist and hip circumferences were determined using an anthropometric measuring tape and the National Institutes for Health protocol.[47(pp7-13)48]

Full-body DXA scans were taken using a Hologic Discovery A DXA system and Hologic QDR software or a GE Healthcare Lunar Prodigy DXA and GE Healthcare enCORE software to assess percent body fat, lean body mass, and fat mass. Percent body fat was calculated as 100% × [fat mass/(fat mass + lean mass)]. Subcutaneous abdominal fat and intra-abdominal fat were measured from computed tomographic scans of 4 single slices centered at the umbilicus using a Philips Brilliance Big Bore or a Toshiba Aquilion. Data were transferred to our study radiologist (A.D.) at the Cross Cancer Institute, Edmonton, who reviewed each scan and used image analysis software (Aquarius Intuition by TeraRecon, Inc) to demarcate and quantify subcutaneous and intra-abdominal fat.

Sample Size

Sample size calculations were based on the standard 2-sample mean comparison formula[49(pp301-304)] with $\alpha = .05$ (2 sided) for the comparison of mean 12-month changes with no adjustment for baseline values. The exercise dose effect on total body fat was the primary outcome of interest. Total body fat was measured in absolute (kilograms) and relative (percent body fat) scales. Expected standard deviations and intervention effects were based on estimated values from the ALPHA Trial.[36] Initially a sample size of 150 participants per group was chosen, allowing 95% power to detect a group difference of 2.6% in percent fat change and 3.8% in fat mass change. Allowing 10% loss to follow-up, sample size was increased to 165 per group. Ultimately, 200 participants per group were randomized given a higher-than-expected volunteer response, providing 95% power to detect group differences of 2.3% and 3.3% in percent fat change and fat mass change, respectively.

Statistical Analysis

Baseline characteristics were compared between groups using 2-sample *t* tests for continuous variables or χ^2 tests for categorical variables. Mean adherence was characterized separately for moderate- and high-volume groups and was calculated as mean exercise minutes per week recorded in exercise logs, weeks 1 through 52, and also between weeks 13 and 52 after the initial 12-week ramp-up period. Mean exercise time spent at 65% to 75% of heart rate reserve (from heart rate monitors) was similarly described. Differences in 12-month change in hypothesized confounding and/or mediating variables were compared between randomization groups using 2-sample *t* tests. All statistical tests were 2 sided with a significance level of .05. Analyses were performed using SAS (SAS 9.2 for Linux, SAS Institute Inc) and graphics were produced using R (R version 3.1.1 for Windows).

Intention to Treat

The intention-to-treat primary analysis was based on least-squares mean differences in 12-month adiposity changes between moderate- and high-volume groups derived from linear models adjusted for baseline adiposity and study location (Edmonton or Calgary). Sensitivity analyses excluded participants who self-reported more than 1000 kcal/d change in past-year energy intake, and also replaced missing 12-month adiposity values with baseline values.

Effect modification by baseline age (continuous) and BMI (continuous) was assessed using statistical tests for

interaction and linear models that predicted 12-month adiposity change. Covariates baseline adiposity, study location (Calgary or Edmonton), and randomization group were included in the models, as well as interaction terms between randomization group and baseline BMI or age. To describe interactions, least-squares mean group changes were calculated, stratified by BMI (<30, ≥30) or age (<60, ≥60 years).

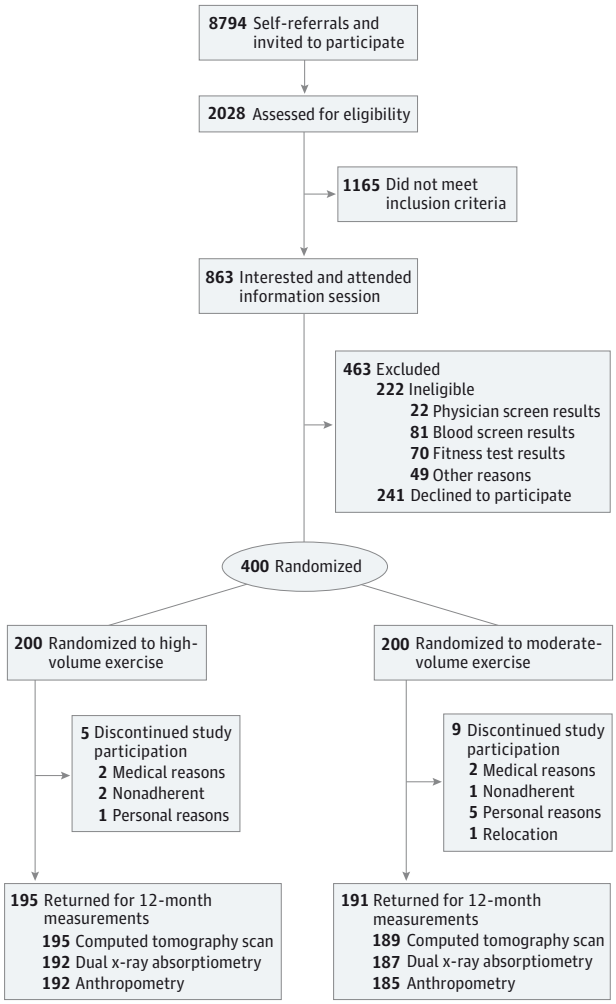
Exploratory

A per-protocol analysis was undertaken, repeating the primary analysis only for women who were exercise adherent, ie, 90% to 100% of prescription for the moderate-volume group (135-150 min/wk) or a mean of at least 90% of prescription for the high-volume group (≥270 min/wk), weeks 13 to 52, based on exercise logs. Also, in an exploratory dose-response analysis that combined the 2 intervention groups, tests for linear trend were performed relating adiposity percentage change to 3 categories of exercise adherence (weeks 1-52); categories corresponded to cut points associated with weight loss (≤150, >150 to <250, ≥250 min/wk).[4]

Results

Participants were recruited from June 2010 through April 2012. The trial concluded by June 2013 when all participants had completed 12-month interventions. Of 400 randomized women, 384 (96.0%) provided baseline and 12-month measurements for at least 1 adiposity outcome (**Figure**). Drop-out rates were 2.5% and 4.5% for the high- and moderate-volume groups, respectively. No serious adverse events were reported. There were no significant differences between groups at baseline except for ethnicity (**Table 1**). The mean BMI was consistent with an overweight population, and the mean age was 59 years (5% were older than 70 years).

Figure. Consolidated Standards of Reporting Trials (CONSORT) Diagram: Flow of Participants Through the Breast Cancer and Exercise Trial in Alberta, Alberta, Canada, 2010 Through 2013



Adherence

Median (interquartile range) adherence for the moderate- and high-volume groups was 129 (106-138) and 228 (156-262) min/wk, respectively, during the 52-week period. Excluding the ramp-up period, adherence was 137 (111-150) and 254 (166-290) min/wk, respectively, representing 91% and 85% of targeted amounts. Additional adherence data are provided in eTable 1 in Supplement 2. The median (interquartile range) intense exercise time according to heart rate monitors (excluding the ramp-up period) was 88 (53-115) and 128 (66-185) min/wk for the moderate- and high-volume groups, respectively, representing 59% and 43% of prescribed durations.

During the 12-month period, total recreational activity increased more in the high- vs moderate-volume group (26.5 vs 14.2 MET-h/wk; $P < .001$), as did estimated $\dot{V}O_{2max}$ (5.09 vs 3.96 L/kg × min; $P = .05$). Women in the 2 groups engaged in similar activities within the exercise prescription (eTable 2 in Supplement 2). Supervised activities accounting for more than 75% of log entries were use of the elliptical trainer, walking, and bicycling. Home-based activities accounting for more than 70% of log entries were walking, elliptical trainer use, and running. There were no group differences in 12-month mean changes in energy intake ($P = .48$), dietary fat intake ($P = .53$), or nonrecreational physical activity (occupational activity, $P = .68$; household activity, $P = .76$; walking or biking to or from work, $P = .29$).

Intention-to-Treat Analysis

Least-squares mean reductions in total body fat were significantly larger in the high- vs moderate-volume group (−2.41 [95% CI, −2.97 to −1.85] vs −1.45 [95% CI, −2.01 to −0.89] kg, $P = .01$; −2.2% [95% CI, −2.6% to −1.7%] vs −1.2% [95% CI, −1.7% to −0.7%], $P = .002$) (**Table 2**). Subcutaneous abdominal fat also decreased significantly more in the high-volume group, as well as total abdominal fat, BMI, waist circumference, and waist to hip ratio (Table 2). Weight change ranged from more than 3% weight gain (9% of moderate-volume group, 6% of high-volume group) to more than 5% weight loss (27% of moderate-volume group, 34% of high-volume group); mean weight

Table 1. Participant Baseline Characteristics in the Breast Cancer and Exercise Trial in Alberta, Alberta, Canada, 2010 Through 2013

Baseline Characteristic	Moderate Volume (n = 200)	High Volume (n = 200)	*P* Value
Employed full time, No. (%)	59 (29.5)	71 (35.5)	.20
Educated beyond high school, No. (%)	155 (77.5)	155 (77.5)	>.99
Married or common-law, No. (%)	139 (69.5)	136 (68.0)	.75
White race, No. (%)	186 (93.0)	172 (86.0)	.02
Age, mean (SD), y	59.5 (5.1)	59.4 (4.8)	.81
Total energy intake, mean (SD), kcal/d	1474.0 (541.4)	1462.1 (588.2)	.83
Past year physical activity, mean (SD), MET-h/wk[a]			
Total	96.4 (48.2)	93.7 (44.1)	.57
Recreational	9.9 (13.6)	8.5 (9.4)	.22
Maximal oxygen consumption, mean (SD), mL/kg/min	26.8 (5.0)	26.7 (5.3)	.84
Weight, mean (SD), kg	77.4 (13.0)	77.3 (13.0)	.97
BMI, mean (SD)	29.4 (4.4)	29.1 (4.4)	.41
Circumference, mean (SD), cm			
Waist	98.6 (10.8)	98.7 (11.0)	.97
Hip	109.9 (10.0)	109.4 (9.9)	.64
DXA measurements, mean (SD)			
Body fat, %	40.7 (5.9)	40.5 (5.8)	.72
Total fat mass, kg	31.0 (8.7)	30.8 (8.6)	.80
Total lean mass, kg	44.0 (5.7)	44.1 (5.5)	.90
CT-measured fat area, mean (SD), cm^2			
Intra-abdominal	133.4 (49.3)	125.6 (50.8)	.12
Subcutaneous	313.8 (99.0)	314.1 (97.9)	.98
Intra-abdominal + subcutaneous	447.3 (131.2)	439.8 (130.9)	.57

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CT, computed tomography; DXA, dual x-ray absorptiometry; MET, metabolic equivalent.

[a] Self-reported in the Past Year Total Physical Activity Questionnaire.

Table 2. Changes in Adiposity Between Baseline and 12 Months in the Breast Cancer and Exercise Trial in Alberta, Alberta, Canada, 2010 Through 2013

	Moderate Volume		High Volume			
Adiposity Measure	No.[a]	LS Mean Change (95% CI)[b]	No.[a]	LS Mean Change (95% CI)[b]	LS Mean Difference (95% CI)[c]	*P* Value[d]
Weight, kg	185	−1.79 (−2.46 to −1.11)	192	−2.52 (−3.19 to −1.85)	−0.73 (−1.62 to 0.15)	.11
BMI	185	−0.70 (−0.95 to −0.44)	192	−1.05 (−1.31 to −0.80)	−0.36 (−0.69 to −0.02)	.04
Circumference, cm						
Waist	185	−4.37 (−5.33 to −3.41)	192	−5.66 (−6.61 to −4.71)	−1.29 (−2.55 to −0.03)	.05
Hip	185	−2.14 (−2.87 to −1.42)	192	−2.39 (−3.11 to −1.68)	−0.25 (−1.20 to 0.70)	.61
Waist to hip ratio	185	−0.025 (−0.031 to −0.018)	192	−0.034 (−0.041 to −0.027)	−0.009 (−0.018 to 0.000)	.04
DXA measurements						
Total lean mass, kg	187	−0.31 (−0.59 to −0.04)	192	0.00 (−0.28 to 0.27)	0.31 (−0.05 to 0.68)	.09
Body fat, %	187	−1.2 (−1.7 to −0.7)	192	−2.2 (−2.6 to −1.7)	−1.0 (−1.6 to −0.4)	.002
Total fat mass, kg	187	−1.45 (−2.01 to −0.89)	192	−2.41 (−2.97 to −1.85)	−0.96 (−1.71 to −0.22)	.01
CT-measured fat area, cm^2						
Intra-abdominal	189	−11.9 (−15.2 to −8.64)	195	−13.4 (−16.7 to −10.2)	−1.50 (−5.85 to 2.85)	.50
Subcutaneous	189	−23.7 (−30.2 to −17.1)	195	−34.5 (−41.0 to −28.0)	−10.8 (−19.5 to −2.16)	.01
Intra-abdominal + subcutaneous	189	−35.6 (−44.2 to −26.9)	195	−47.8 (−56.4 to −39.1)	−12.2 (−23.7 to −0.70)	.04

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CT, computed tomography; DXA, dual x-ray absorptiometry; LS, least-squares.

[a] Number of women completing measures at baseline and 12 months, for whom a change could be calculated, within each randomization group.

[b] Values are in the form of least-squares mean (lower 95% confidence limit to upper 95% confidence limit) based on the model, adiposity change = β_0 + β_1(adiposity at baseline) + β_2(location) + β_3(randomization group), where adiposity at baseline corresponds to the adiposity outcome modeled.

[c] Least-squares estimate of the difference between moderate- and high-volume groups, using model specified in footnote b.

[d] *P* value derived from model specified in footnote b, and corresponds to the null hypothesis that the LS mean difference between high- and moderate-volume groups equals 0 against the 2-sided alternative hypothesis.

Table 3. Changes in Adiposity in Each Intervention Group Stratified by Baseline Body Mass Index in the Breast Cancer and Exercise Trial in Alberta (BETA), Alberta, Canada, 2010 Through 2013

Adiposity Measure	BMI	Moderate Volume		High Volume		LS Mean Difference (95% CI)[c]	*P* Value for Interaction[d]
		No.[a]	LS Mean Change (95% CI)[b]	No.[a]	LS Mean Change (95% CI)[b]		
Weight, kg	<30	114	−1.81 (−2.49 to −1.14)	119	−1.68 (−2.35 to −1.01)	0.13 (−0.74 to 1.01)	.02
	≥30	71	−1.74 (−3.13 to −0.34)	73	−3.83 (−5.19 to −2.48)	−2.10 (−3.94 to −0.26)	
BMI	<30	114	−0.68 (−0.94 to −0.43)	119	−0.73 (−0.99 to −0.48)	−0.05 (−0.38 to 0.28)	.03
	≥30	71	−0.72 (−1.26 to −0.18)	73	−1.56 (−2.08 to −1.04)	−0.84 (−1.55 to −0.13)	
Circumference, cm							
Waist	<30	114	−4.05 (−5.15 to −2.95)	119	−4.30 (−5.41 to −3.20)	−0.26 (−1.69 to 1.18)	.01
	≥30	71	−4.93 (−6.67 to −3.18)	73	−7.82 (−9.51 to −6.12)	−2.89 (−5.19 to −0.59)	
Hip	<30	114	−2.35 (−3.04 to −1.65)	119	−1.73 (−2.43 to −1.04)	0.61 (−0.29 to 1.52)	.04
	≥30	71	−1.68 (−3.21 to −0.16)	73	−3.40 (−4.86 to −1.94)	−1.71 (−3.72 to 0.29)	
Waist to hip ratio	<30	114	−0.020 (−0.029 to −0.012)	119	−0.029 (−0.038 to −0.021)	−0.009 (−0.020 to 0.002)	.17
	≥30	71	−0.031 (−0.042 to −0.020)	73	−0.041 (−0.052 to −0.030)	−0.010 (−0.024 to 0.005)	
DXA measurements							
Total lean mass, kg	<30	114	−0.10 (−0.42 to 0.22)	118	0.41 (0.10 to 0.73)	0.51 (0.10 to 0.92)	.22
	≥30	73	−0.60 (−1.11 to −0.08)	74	−0.66 (−1.17 to −0.14)	−0.06 (−0.74 to 0.62)	
Body fat, %	<30	114	−1.5 (−2.0 to −1.0)	118	−2.3 (−2.9 to −1.8)	−0.8 (−1.5 to −0.1)	.55
	≥30	73	−0.4 (−1.3 to 0.4)	74	−1.7 (−2.5 to −0.8)	−1.2 (−2.4 to −0.1)	
Total fat mass, kg	<30	114	−1.60 (−2.14 to −1.06)	118	−2.02 (−2.56 to −1.48)	−0.42 (−1.13 to 0.29)	.07
	≥30	73	−1.15 (−2.32 to 0.02)	74	−2.97 (−4.12 to −1.82)	−1.82 (−3.38 to −0.26)	
CT-measured fat area, cm^2							
Intra-abdominal	<30	114	−11.0 (−14.9 to −7.08)	121	−12.2 (−16.1 to −8.25)	−1.17 (−6.32 to 3.98)	.55
	≥30	75	−13.5 (−19.3 to −7.68)	74	−16.2 (−22.0 to −10.4)	−2.72 (−10.5 to 5.05)	
Subcutaneous	<30	114	−24.7 (−32.3 to −17.1)	121	−29.7 (−37.2 to −22.1)	−4.95 (−14.9 to 4.97)	.03
	≥30	75	−24.6 (−35.9 to −13.3)	74	−44.7 (−56.0 to −33.4)	−20.1 (−35.3 to −4.91)	
Intra-abdominal + subcutaneous	<30	114	−35.7 (−45.6 to −25.8)	121	−41.7 (−51.6 to −31.7)	−5.96 (−19.0 to 7.03)	.07
	≥30	75	−38.9 (−54.1 to −23.6)	74	−61.7 (−76.9 to −46.5)	−22.9 (−43.3 to −2.42)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CT, computed tomography; DXA, dual x-ray absorptiometry; LS, least-squares.

[a] No. represents the number of women completing measures at baseline and 12 months to for whom a change could be calculated to within each randomization group.

[b] Values are in the form of least-squares mean (lower 95% confidence limit to upper 95% confidence limit) based on the model, adiposity change = β_0 + β_1(adiposity at baseline) + β_2(location) + β_3(randomization group), where adiposity at baseline corresponds to the adiposity outcome modeled.

[c] Least-squares estimate of the difference between moderate-volume and high-volume groups, using model specified in footnote b.

[d] *P* value for interaction corresponds to the test for interaction between randomization group and baseline BMI based on the following model: adiposity change = β_0 + β_1(adiposity at baseline) + β_2(location) + β_3(randomization group) + β_4(baseline BMI) + β_5(baseline BMI × randomization group), where BMI was treated as a continuous covariate and adiposity at baseline corresponds to the adiposity outcome modeled. For the outcome of BMI change, β_4 was excluded from the model.

changes were −2.5% (moderate volume) and −3.3% (high volume), corresponding to −1.79 (95% CI, −2.46 to −1.11) and −2.52 (95% CI, −3.19 to −1.85) kg, respectively (Table 2). A sensitivity analysis excluding 10 women who did not adhere to dietary instructions had a negligible impact on primary results. Replacing missing 12-month adiposity measures with baseline values (n = 11 to 15 in moderate-volume group; n = 5 to 8 in high-volume group) also had little impact.

Significant interactions were found between randomization group and baseline BMI (**Table 3**), showing stronger dose-response effects for obese women (BMI ≥ 30) with respect to weight, BMI, waist and hip circumference, and subcutaneous abdominal fat changes. No significant interactions were found with baseline age except for intra-abdominal fat change (*P* for interaction = .02); women younger than 60 years experienced greater reductions with the high-volume prescription, whereas women 60 years or older experienced greater reductions with the moderate-volume prescription.

Exploratory Analyses

In a per-protocol analysis of 138 adherent women (**Table 4**), least-squares mean changes in total fat were −3.63 (95% CI, −4.52 to −2.75) kg vs −1.86 (95% CI, −2.90 to −0.82) kg (*P* = .005), or −3.4% (95% CI, −4.3% to −2.6%) vs −1.3% (95% CI, −2.3% to −0.4%; *P* < .001), for high- and moderate-volume groups, respectively. Similarly for BMI, waist circumference, and subcutaneous, intra-abdominal, and total abdominal fat, mean changes were significantly larger for the high-volume group. In an exploratory analysis that combined intervention groups, favorable dose-response trends were observed between exercise adherence and adiposity per-

Table 4. Changes in Adiposity Between Baseline and 12 Months in a Per-Protocol Analysis of Adherent Participants[a] in the Breast Cancer and Exercise Trial in Alberta, Alberta, Canada, 2010 Through 2013

	Moderate		High			
Adiposity Measure	No.[b]	LS Mean Change (95% CI)[c]	No.[b]	LS Mean Change (95% CI)[c]	LS Mean Difference (95% CI)[d]	*P* Value[e]
Weight, kg	58	−2.41 (−3.57 to −1.25)	80	−3.67 (−4.67 to −2.67)	−1.25 (−2.64 to 0.13)	.08
BMI	58	−0.89 (−1.34 to −0.44)	80	−1.58 (−1.97 to −1.19)	−0.69 (−1.23 to −0.15)	.01
Circumference, cm						
Waist	58	−5.00 (−6.82 to −3.17)	80	−7.35 (−8.93 to −5.77)	−2.35 (−4.53 to −0.18)	.03
Hip	58	−2.77 (−3.92 to −1.62)	80	−3.74 (−4.72 to −2.75)	−0.97 (−2.33 to 0.40)	.16
Waist to hip ratio	58	−0.023 (−0.037 to −0.010)	80	−0.039 (−0.050 to −0.027)	−0.016 (−0.032 to 0.000)	.05
DXA measurements						
Total lean mass, kg	58	−0.61 (−1.11 to −0.12)	80	−0.06 (−0.49 to 0.38)	0.56 (−0.03 to 1.14)	.06
Body fat, %	58	−1.3 (−2.3 to −0.4)	80	−3.4 (−4.3 to −2.6)	−2.1 (−3.2 to −1.0)	<.001
Total fat mass, kg	58	−1.86 (−2.90 to −0.82)	80	−3.63 (−4.52 to −2.75)	−1.78 (−3.00 to −0.55)	.005
CT-measured fat area, cm^2						
Intra-abdominal	58	−10.9 (−16.5 to −5.29)	80	−18.3 (−23.2 to −13.4)	−7.39 (−14.1 to −0.66)	.03
Subcutaneous	58	−21.5 (−33.3 to −9.71)	80	−44.2 (−54.4 to −33.9)	−22.7 (−36.7 to −8.62)	.002
Intra-abdominal + subcutaneous	58	−32.7 (−47.6 to −17.8)	80	−62.3 (−75.3 to −49.3)	−29.6 (−47.4 to −11.8)	.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CT, computed tomography; DXA, dual x-ray absorptiometry; LS, least-squares.

[a] Women assigned to the moderate-volume group were adherent if they completed 90% to 100% of the exercise prescription (mean, 135-150 min/wk), weeks 13 to 52 at full prescription; women assigned to the high-volume group were adherent if they completed at least 90% of the exercise prescription (mean, ≥270 min/wk), weeks 13 to 52 at full prescription.

[b] Number of women completing baseline and 12-month measurements, for whom change could be calculated, within each randomization group.

[c] Values are in the form of least-squares mean (lower 95% confidence limit to upper 95% confidence limit) based on the model, adiposity change = β0 + β1(adiposity at baseline) + β2(location) + β3(randomization group), where adiposity at baseline corresponds to the adiposity outcome modeled.

[d] Least-squares estimate of the difference between moderate- and high-volume groups using model specified in footnote c.

[e] *P* value derived from model specified in footnote c and corresponds to the null hypothesis that the LS mean difference between high- and moderate-volume groups equals 0 against the 2-sided alternative hypothesis.

cent change (eFigure in Supplement 2); the greatest reductions occurred in women reporting more than 250 min/wk of exercise.

Discussion

During a 12-month period, inactive postmenopausal women with BMI of 22 to 40 prescribed 300 vs 150 min/wk of moderate to vigorous aerobic exercise experienced a significantly greater reduction in mean total body fat (by 1 kg or 1% body fat). Mean reductions in BMI, waist circumference, waist to hip ratio, subcutaneous abdominal fat, and total abdominal fat were also significantly greater in the group prescribed 300 min/wk. Dose-response effects were stronger for obese women (BMI ≥ 30) with respect to change in weight, BMI, waist and hip circumference, and subcutaneous abdominal fat.

The 2% total fat loss achieved in BETA during a 12-month period with 300 min/wk approximated[36,50,51] or exceeded[52,53] reductions in similar trials prescribing 150 to 225 min/wk moderate to vigorous exercise to postmenopausal women. In the Dose-Response to Exercise in Postmenopausal Women (DREW) RCT (n = 464), no dose-response effect was found for reducing body weight or percent body fat.[26,35] However, exercise in DREW was of lower intensity (50% $\dot{V}O_{2max}$) and duration than in BETA, averaging 72, 136, and 192 min/wk in 3 exercise groups vs controls. Three additional dose-comparison RCTs compared walking durations for reducing postmenopausal adiposity,[25,27,34] but only 1 small pilot study (n = 26)[27] showed a dose-response effect, with mean fat reductions of approximately 3% to 4% and 1% to 2% for 225 and 150 min/wk prescriptions, respectively. Collectively, these findings support the use of aerobic exercise for at least 225 min/wk for greater reductions in postmenopausal total body fat.

Adipose tissue is an immunologically[54] and metabolically active endocrine organ[55] that is a source of inflammatory cytokines, adipokines, oxidative stress, and notably, the primary source of sex hormones after menopause,[56] which are proposed[57-61] biomarkers for breast cancer risk. We showed previously in postmenopausal women that total fat loss mediated exercise-induced changes in circulating estradiol and sex hormone binding globulin concentrations[62] and that decreased levels of leptin[63] and C-reactive protein[64] related to total fat loss. Hence, our findings for total fat loss are consistent with decreased breast cancer risk, possibly through these mechanisms.

Abdominal fat warrants separate evaluation because exercise may exert different effects on abdominal vs total fat,[65] and abdominal fat is a risk factor for postmenopausal breast, pancreatic, and endometrial cancers.[17] It is unclear whether visceral obesity increases postmenopausal breast cancer risk, although there is biologic plausibility[66] given its association with insulin resistance, type 2 diabetes, and the metabolic

syndrome,[67,68] which are proposed causal mechanisms.[69-71] Our primary analysis showed no dose-response effect for intra-abdominal fat, with both groups experiencing mean reductions of approximately −12 to −13 cm^2, similar to ALPHA Trial participants (−16.5 cm^2)[36] but superior to other comparable trials.[53,72] A stronger group difference in the per-protocol analysis (−10.9 vs −18.3 cm^2) suggests possibly that nonadherence contributed to our null findings. Other explanations might include effect modification by age, similar exercise intensities,[73,74] or insufficiently high exercise prescriptions.[75]

In contrast, clear benefit was found from prescribing 300 vs 150 min/wk for subcutaneous abdominal fat reduction, with a mean reduction in the high-volume group (−34.5 cm^2) comparable to that of exercisers in ALPHA (−32.0 cm^2)[36] but larger than in other postmenopausal trials.[53,72] Previous dose comparison RCTs in postmenopausal women[25,27,34,35] did not assess subcutaneous abdominal fat, although some reported waist circumference, which is related.[76] The DREW trial[35] (<200 min/wk, 50% $\dot{V}O_{2max}$) reported no dose-response effect for waist circumference, whereas Dalleck et al[27] reported greater reductions prescribing 225 vs 150 min/wk of walking. A post hoc analysis by Bergstrom et al[77] demonstrated the greatest waist reductions for women adhering to 210 min/wk aerobic exercise. Therefore, similar to total body fat, greater reductions in postmenopausal subcutaneous abdominal fat might be achieved with more than 200 min/wk higher-intensity aerobic exercise. Although the clinical significance of subcutaneous abdominal (vs visceral) fat is unclear and somewhat controversial,[78,79] correlations between subcutaneous abdominal fat and cardiometabolic risk factors are evident in women.[79-82] Postmenopausal weight loss has induced favorable changes in the expression of proposed gene biomarkers of cancer risk within subcutaneous abdominal fat.[83]

Exercise-induced weight loss varies widely between individuals,[84,85] which was apparent in BETA. For example, 29 women experienced more than 3% weight gain. Compensatory changes in total energy expenditure or energy intake can occur during exercise intervention trials,[35,86,87] particularly at higher exercise volumes,[35] but an analysis exploring compensation was beyond the scope of this report. Future exercise efficacy trials may incorporate a weight maintenance diet in their protocol, as described recently,[33] to minimize this effect. Effect modification might further explain heterogeneity because obese women in BETA experienced more benefit from the 300 min/wk prescription. Obese women may experience more dramatic dose-response effects given a greater propensity for fat loss. Moreover, dose-response effects varied by age with respect to intra-abdominal fat. Whereas the reason for this effect is unclear, previous studies showed that younger (<70 years) vs older (70-79 years) postmenopausal women experienced greater reductions in total fat[52,88] and intra-abdominal fat[52] over time with increasing aerobic activity.

Experimental evidence from well-powered RCTs is required to support physical activity recommendations, and BETA provides this evidence. To our knowledge, BETA is the largest long-term RCT to compare exercise doses of more than 225 min/wk in healthy postmenopausal women and the first dose-comparison RCT to assess changes in postmenopausal subcutaneous and intra-abdominal fat. Moreover, BETA had exceptional power of 95% to detect small group differences in total body fat change, our primary outcome. A limitation of BETA was that we did not evaluate 420 min/wk (recommended for cancer prevention[17]) because of adherence concerns, and consequently, our results do not reflect the entirety of the dose-response curve. Our results may not generalize to type 2 diabetics, women with uncontrolled hypercholesterolemia, or hormone therapy users because of exclusion criteria.[37] Our study included postmenopausal women with BMI of 22 to 40 who were mostly younger than 70 years old and motivated to exercise. Yet adherence was challenging; 22.5% of women in the high-volume group exercised less than a mean of 150 min/wk at full prescription, which likely attenuated dose-response effects in the intention-to-treat analysis. Nonadherence should be considered when sample size requirements are calculated for future exercise trials that test higher volumes or intensities of exercise.

Conclusions

A probable association between physical activity and postmenopausal breast cancer risk[17,18] is supported by more than 100 epidemiologic studies, with strong biologic rationale supporting fat loss as an important (though not the only) mediator of this association.[57-59] Our findings of a dose-response effect of exercise on total fat mass and several other adiposity measures including abdominal fat, especially in obese women, provide a basis for encouraging postmenopausal women to exercise at least 300 min/wk, longer than the minimum recommended for cancer prevention.[1,3,17,89,90] We recognize that exercise alone may not suffice for achieving, for example, a 10% weight loss target in obese women.[91,92] However, the optimal dose for breast cancer prevention should also be informed by effects on other mediating pathways besides adiposity and ideally, evidence from an RCT with breast cancer end points. One meta-analysis estimated a 33% increase in estrogen receptor–positive/progesterone receptor–positive postmenopausal breast cancer risk with every 5-unit increase in BMI.[21] Given the mean BMI reductions in BETA, 4.6% and 6.9% breast cancer risk reductions may occur for women prescribed 150 vs 300 min/wk of aerobic exercise, an added dose benefit of 2.3%. In obese women, the added dose benefit may be greater, approximately 5.5%, given 4.8% and 10.3% risk reductions with 150- vs 300-min/wk prescriptions. Exploratory analyses suggest that some of our results were attenuated by modest adherence; that intra-abdominal fat change may follow a different dose-response curve than total body fat, possibly warranting a different exercise prescription or dietary modification; and that 300 vs 150 min/wk may provide different benefit depending on BMI and age. Research examining different exercise prescriptions, individual propensity for fat loss, tendency toward exercise compensation, and predictors of exercise adherence may enhance the impact of a higher vs lower exercise prescription.

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Author Affiliations: Department of Cancer Epidemiology and Prevention Research, CancerControl Alberta, Alberta Health Services, Calgary, Alberta, Canada (Friedenreich, Neilson, O'Reilly); Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada (Friedenreich); Cross Cancer Institute, CancerControl Alberta, Alberta Health Services, Edmonton, Alberta, Canada (Duha); School of Public Health, University of Alberta, Edmonton, Alberta, Canada (Yasui); Faculty of Physical Education and Recreation, University of Alberta, Edmonton, Alberta, Canada (Morielli, Adams, Courneya).

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Study concept and design: Friedenreich, Courneya.
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Drafting of the manuscript: Friedenreich, Neilson, O'Reilly, Courneya.
Critical revision of the manuscript for important intellectual content: Friedenreich, Neilson, Duha, Yasui, Morielli, Adams, Courneya.
Statistical analysis: Friedenreich, O'Reilly, Yasui, Courneya.
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Invited Commentary

Exercise and Cancer Risk—How Much Is Enough?

Kerri Winters-Stone, PhD

The health benefits of regular physical activity are clear, providing a seemingly simple approach to improving public health. Evidence for the benefits of exercise for the prevention of age-related diseases, including cancer, has been accumulating for quite some time and the question of whether exercise is beneficial has largely been answered. There are current public health guidelines calling for adults to engage in at least 150 minutes of moderate-intensity aerobic activity per week to reach the minimum target of exercise that is linked to reduced risk of chronic disease.[1] However, there is less evidence to draw from that might support extending the recommendations to include an upper range of exercise that could optimize public health outcomes. Establishing the dose-response relationship of exercise is just like that for pharmacologic therapy—we need to know the minimum effective dose, whether there is a dose-response relationship, and when the point of diminishing returns might be reached. This first question is what led to current public health guidelines for exercise. Rigorously designed and executed dose-response exercise trials will help us answer the next two.

Related article page 766

In this issue of *JAMA Oncology*, Friedenreich et al[2] report on a dose-response trial comparing the effects of the currently recommended amount of aerobic exercise (150 min/wk) to twice that volume (300 min/wk) on body weight and composition in postmenopausal women. Postmenopausal weight gain and adiposity are known risk factors for chronic illnesses, particularly breast cancer, and exercise is thought to protect against these illnesses in part by influencing weight regulation.[3] Although prior dose-response studies of exercise and body weight and/or composition have been conducted, reports have been conflicting and notable limitations in the design and execution of previous studies have confounded the ability to reach consensus about optimal doses of exercise. In contrast to previous work, Friedenreich et al[2] designed and executed a nearly definitive trial that was more