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ORIGINAL REPORT

Alberta Physical Activity and Breast Cancer Prevention Trial: Sex Hormone Changes in a Year-Long Exercise Intervention Among Postmenopausal Women

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A B S T R A C T

Purpose
We examined how an aerobic exercise intervention influenced circulating estradiol, estrone, sex hormone–binding globulin (SHBG), androstenedione, and testosterone levels, which may be involved in the association between physical activity and breast cancer risk.

Methods
A two-center, two-arm randomized controlled trial of exercise was conducted in 320 postmenopausal, sedentary women age 50 to 74 years. Participants were randomly assigned to a 1-year aerobic exercise intervention of 225 min/wk (n = 160) or to a control group who maintained their usual level of activity (n = 160). Baseline, 6-month, and 12-month assessments of estrone, estradiol, androstenedione, and testosterone were quantified by radioimmunoassay after extraction, and SHBG was quantified by an immunometric assay. Intent-to-treat analyses were performed using linear mixed models.

Results
Blood data were available on 309 women (96.6%) at 12 months. Women in the intervention group exercised an average of 3.6 d/wk for 178 min/wk. At 12 months, statistically significant reductions in estradiol (treatment effect ratio [TER] = 0.93; 95% CI, 0.88 to 0.98) and free estradiol (TER = 0.91; 95% CI, 0.87 to 0.96) and increases in SHBG (TER = 1.04; 95% CI, 1.02 to 1.07) were observed in the exercise group compared with the control group. No significant differences in estrone, androstenedione, and testosterone levels were observed between exercisers and controls at 12 months.

Conclusion
This trial found that previously sedentary postmenopausal women can adhere to a moderate- to vigorous-intensity exercise program that results in changes in estradiol and SHBG concentrations that are consistent with a lower risk for postmenopausal breast cancer.

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INTRODUCTION

Consistent observational epidemiologic evidence suggests that physical activity is associated with reduced postmenopausal breast cancer risk.[1-3] Several plausible biologic mechanisms have been hypothesized to underlie this association, but none have been established yet.[4] Multiple inter-related mechanisms are likely operative,[5] including changes in metabolic and sex hormones,[6] growth factors,[7] adiposity,[8] and possibly immune function.[9]

One of the most plausible mechanisms is via the modification of sex hormone levels. High endogenous estrogen and androgen levels are fairly consistently associated with an increase in breast cancer risk,[10-12] whereas increased sex hormone–binding globulin (SHBG) levels are associated with a decrease in risk.[12] Previous studies in postmenopausal women, all but two of which were observational, have also observed that serum sex hormone concentrations decrease[12-19] and SHBG concentrations increase[13,20] with increasing physical activity; several mechanisms may be involved, including preventing weight gain after menopause.[13-16,21,22]

To provide more direct evidence regarding the biologic mechanisms than observational studies can

provide, we conducted the Alberta Physical Activity and Breast Cancer Prevention Trial, a two-center, two-arm randomized controlled trial that examined how a 1-year aerobic exercise intervention, compared with a usual sedentary lifestyle, influences sex hormone concentrations, body composition, mammographic density, insulin-like growth factors, insulin resistance, and markers of obesity and inflammation. In this article, the first from this trial, we report the effects of the exercise intervention on sex hormone concentrations, which were the primary outcomes. Subsequent reports will present results for the other outcomes.

METHODS

Setting and Participants

This trial was conducted at the Westside Recreation Centre in Calgary and at the University of Alberta in Edmonton, Canada. The study and protocol were approved by the institutional review boards at the Alberta Cancer Board and the Universities of Calgary and Alberta, and all participants provided written informed consent. Women from the general population were recruited through targeted mailings to participants in the Alberta Breast Screening Program, via the Alberta Family Physicians Research Network, and through media campaigns. Eligibility criteria were as follows: English speaking; resident of Calgary or Edmonton; age 50 to 74 years; postmenopausal for at least 24 months; no previous cancer diagnosis besides nonmelanotic skin cancer; no major comorbidities; acceptable heart and lung function as assessed by a baseline fitness test; sedentary (< 90 min/wk recreational activity or, if between 90 and 120 min/wk of physical activity, having a maximal oxygen uptake < 34.5 mL/kg/min); able to undertake unrestricted physical activity as assessed by physician[23]; normal levels of fasting lipids, thyroid-stimulating hormone, and ALT; body mass index between 22 and 40 kg/m^2; breast tissue density greater than a zero density level; nonsmoker; alcohol intake less than 14 drinks per week; no medications or exogenous hormones that might influence estrogen metabolism or breast tissue growth; not currently or planning to undertake a weight loss program; and not planning extended absences in the 18 months subsequent to enrollment. Eligibility was determined in several stages and included telephone screening, completion of questionnaires at an information session, a baseline mammogram, physician approval, blood screening, and a submaximal fitness test.

Random Assignment and Blinding

The random assignment sequence was created by the study biostatistician (R.F.B.) using a random number generator program in S-Plus (Version 3.3; Statistical Sciences, Seattle, WA). Random assignment was stratified by center (Calgary or Edmonton) and body mass index (< or ≥ 27.5 kg/m^2), with blocks of random size between four and six. Numbered sealed envelopes were opened by the research coordinator in Calgary at the time of random assignment. All assessments of outcome measures were blinded.

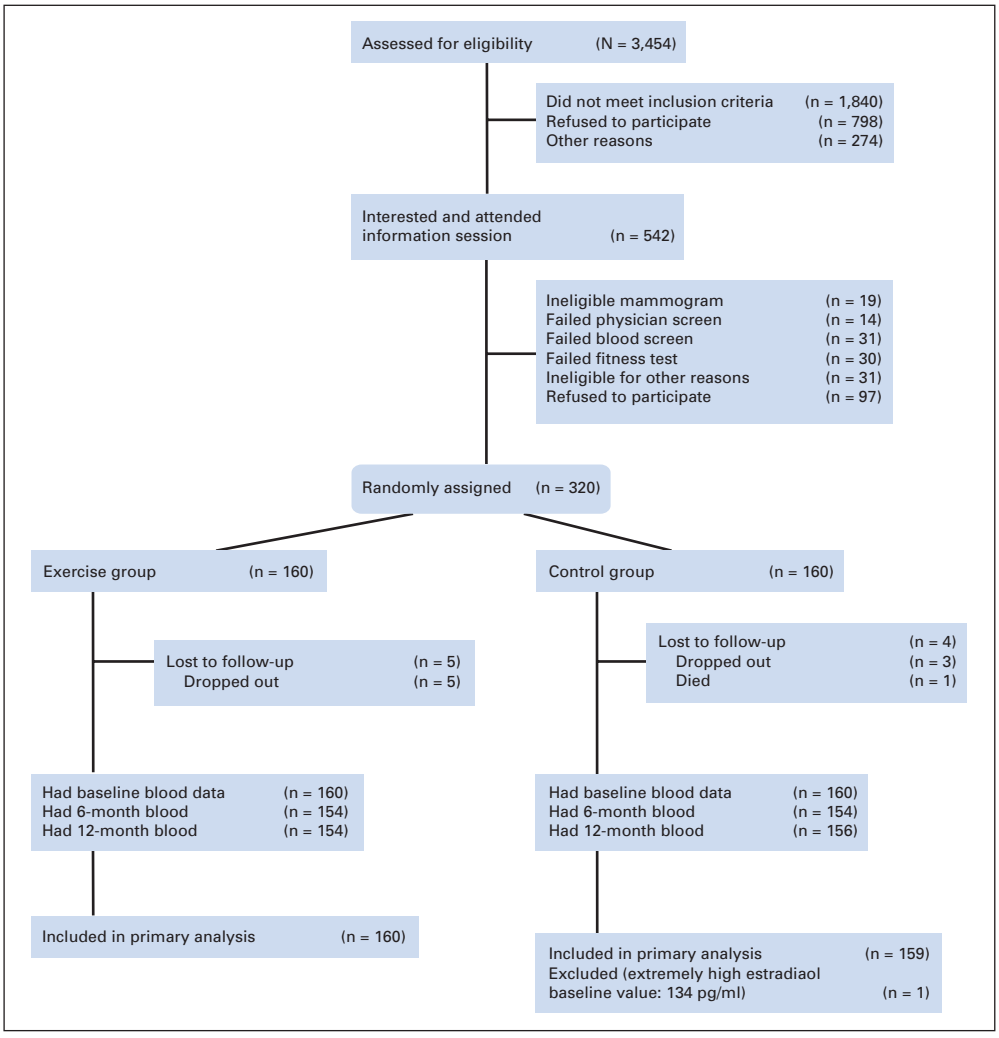

Fig 1. CONSORT diagram showing recruitment of participants into the Alberta Physical Activity and Breast Cancer Prevention Trial.

Table 1. Baseline Demographics and Clinical Characteristics of Participants in the ALPHA Trial, Alberta, Canada, 2003-2007

Characteristic	Exercisers (n = 160)	Controls (n = 160)
Age, years		
Mean	61.2	60.6
SD	5.4	5.7
Body mass index, kg/m^2		
Mean	29.1	29.2
SD	4.5	4.3
Alcohol intake, g/d		
Mean	4.4	5.0
SD	5.9	7.6
Total energy intake, kcal/d		
Mean	1,551.2	1,527.3
SD	598.7	535.0
Maximal oxygen consumption, mL/kg/min		
Mean	27.1	26.8
SD	6.2	6.0
Past year total physical activity, MET-h/wk		
Total physical activity		
Mean	114.2	129.1
SD	57.6	77.9
Occupational activity		
Mean	50.4	52.2
SD	49.1	57.9
Household activity		
Mean	52.9	63.9
SD	34.3	53.5
Recreation activity		
Mean	10.2	12.1
SD	11.8	13.6
Full-time employment		
No. of patients	82	79
%	55	51
Education > high school		
No. of patients	112	102
%	70	64
Married/common law		
No. of patients	113	125
%	71	78
White race		
No. of patients	144	145
%	91	91
First-degree family history of breast cancer		
No. of patients	31	35
%	19	22
Ever used hormone therapy		
No. of patients	75	71
%	47	44
Sex hormone–binding globulin, nmol/L		
Median	41.5	39.5
Quartile 1-3	30.0-57.0	28.0-51.5
Estrone, pg/mL		
Median	32.0	32.0
Quartile 1-3	24.0-44.0	22.5-44.5
Estradiol, pg/mL		
Median	9.0	10.0
Quartile 1-3	7.0-12.0	7.0-14.0
Free estradiol, pg/mL		
Median	0.23	0.24
Quartile 1-3	0.17-0.31	0.18-0.36
Androstenedione, pg/mL		
Median	576	547
Quartile 1-3	434-779	417-736
Testosterone, ng/dL		
Median	24.3	23.3
Quartile 1-3	16.8-32.8	17.5-32.4
Free testosterone, ng/dL		
Median	0.36	0.36
Quartile 1-3	0.24-0.48	0.25-0.49

(continued in next column)

Table 1. Baseline Demographics and Clinical Characteristics of Participants in the ALPHA Trial, Alberta, Canada, 2003-2007 (continued)

Abbreviations: ALPHA, Alberta Physical Activity and Breast Cancer Prevention Trial; SD, standard deviation; MET, metabolic equivalent.

Intervention

The exercise intervention was a monitored, structured program of at least 45 minutes of aerobic exercise performed 5 d/wk for 12 months at 70% to 80% heart rate reserve. At least three sessions per week were facility based with on-site exercise trainers, and the remainder of the sessions were home based. During the first 3 months of the intervention, the frequency, duration, and intensity of exercise were gradually increased from the starting level of three sessions a week of 15 to 20 minutes in duration at an intensity of 50% to 60% heart rate reserve to the final prescription achieved in week 12. Participants were instructed to perform at least half of their total workout time within their target heart rate zone. Any exercise could be performed to reach the required intensities.

Interim submaximal fitness tests were performed in the exercise group at weeks 12, 24, 36, and 48 to monitor progress, maintain motivation, and adjust individual exercise prescriptions to ensure continual training effects. Women in the control group were asked to maintain their regular sedentary lifestyle. Both exercise and control participants were also asked not to change their usual diet.

Several methods to increase adherence with the exercise intervention were implemented, including an individualized exercise program, with regularly scheduled sessions and automatic follow-up for missed sessions; plans for sessions missed because of vacations or illness; a comprehensive educational package; group sessions; social interaction; donated incentives awarded at different milestones; regular newsletters; and a study Web site. Control participants received newsletters and a 1-month pass to the fitness center at the end of the study, the educational materials, and time with fitness trainers to plan their own exercise program.

Exercise participants wore heart rate monitors (Polar A3; Polar, Lake Success, NY) and recorded their activities in weekly exercise logs that included type of activity, minutes of exercise completed, average heart rate, and Borg Rating of Perceived Exertion.[24] Adherence was additionally monitored by the exercise trainers who kept separate logs of the same exercise variables. All situations of vacation, illness, or injury were recorded and tracked by the exercise trainers.

Baseline and End-of-Study Measures

Baseline data on demographics, medical and reproductive history, postmenopausal hormone use, and medication and nonprescription drug use were obtained from a self-administered questionnaire. At baseline and the 12-month follow-up, past year dietary intake was obtained using the US National Cancer Institute's 124-item Diet History Questionnaire adapted for use in Canadian populations,[25] and physical activity was obtained using the Past Year Total Physical Activity Questionnaire.[26] Physical fitness was assessed at baseline and at 12 months using a modified Balke treadmill protocol to estimate maximum oxygen consumption from submaximal exercise intensities. Oxygen consumption at the age-predicted

maximum heart rate was estimated by extrapolating from the two last completed stages using the American College of Sports Medicine metabolic equations for estimating oxygen consumption at the workload of each stage.[27]

Blood Collection and Hormone Assays

Blood was collected after a minimum 10-hour fast at baseline (60 mL) and 6 and 12 months (40 mL each) after random assignment, and all medications taken in the past 24 hours were recorded. Blood collections occurred at the Calgary Laboratory Service clinic at the Tom Baker Cancer Centre and at the Cross Cancer Institute in Edmonton. All blood samples were collected, processed, and stored within 12 hours of collection. Blood samples were shipped and stored in our −86°C freezers until the time of the assays.

Laboratory assays were conducted at the Reproductive Endocrine Research Laboratory (University of Southern California, Los Angeles, CA). Each participant's samples from the three time points were included in a single batch, but the order was randomized. Each batch also had an equal number of samples from exercise and control participants with similar random assignment dates and two pooled quality control samples. Total estrone, estradiol, androstenedione, and testosterone levels were quantified by radioimmunoassay after organic solvent extraction and Celite (CAS 68855-54-9; Mallinckrodt Baker, Paris, KY) column partition chromatography.[28-30] Chromatographic separation of the steroids was achieved by using different concentrations of toluene in iso-octane and ethyl acetate in iso-octane. We quantified SHBG via an immunometric assay using the Immulite Analyzer (Siemens Diagnostic Products, Los Angeles, CA). The SHBG concentration and an assumed albumin concentration of 43 g/L were then used in a validated algorithm with total testosterone or total estradiol to calculate free testosterone or free estradiol, respectively.[31,32]

For all analytes, the intrabatch coefficients of variation ranged between 4.0% and 7.5%, whereas the interbatch coefficients of variation ranged between 8.0% and 13%. The lower limits of detection for the assays for androstenedione, testosterone, estrone, estradiol, and SHBG were 0.03 ng/mL, 1.5 ng/dL, 5 pg/mL, 3 pg/mL, and 1 nmol/L, respectively. No woman had undetectable levels.

Statistical Analysis and Sample Size

The sample size calculations were based on the normal theory formula for comparing means of two independent samples.[33] Taking a conservative approach, we considered the comparison of means of 12-month outcomes (log transformed, with no adjustment for baseline values) for the estrogen outcomes. Using preliminary results from the only previous trial[14,34] for the standard deviations (SDs), a sample size of 150 participants per group was selected for an 80% power to detect anticipated changes of 10% to 20% in the three estrogen outcomes at $\alpha = .05$. We enrolled 160 participants per group to allow for study dropouts.

The primary analysis assessed the intervention effect based on assigned group at random assignment regardless of adherence for all participants with complete data at baseline and end of study (intent to treat). All hormones were non-normally distributed, and therefore, analyses were performed on log-transformed values. The intervention effects were evaluated with linear mixed models considering the sex hormone measures at 6 and 12 months as repeated measures. The models included main effects of intervention and time, as well as their interaction term, and were adjusted for baseline values. The intervention effect was denoted by a geometric mean ratio for the exercise group over the control group from the mixed models.

As a secondary analysis, we examined whether or not the effect of exercise on hormone concentrations varied by adherence. We classified exercise adherence into the following three categories predefined by public health guidelines[35,36]: less than 150, 150 to 225, and more than 225 min/wk. To explore the possibility that the effect of exercise on changes in sex hormones was mediated by weight change, we further adjusted our models for weight change at 12 months. All statistical tests were two-sided, with a level of significance set at $P = .05$. Statistical analyses were performed using SAS software (Version 9.1; SAS Institute, Cary, NC).

RESULTS

Study Participants

A total of 3,454 women were assessed for eligibility out of the 4,543 sent letters of invitation and the 2,170 women who responded after the media campaigns and other recruitment methods (Fig 1). Of these women, 1,840 did not meet the inclusion criteria, 798 refused participation, and 274 were excluded for other reasons including loss of contact. The main reasons for refusal to participate were lack of interest in the study (n = 574), unwillingness to be randomly assigned (n = 105), withdrawal before the information session (n = 48), and lack of time (n = 71). Of the 542 women who attended an information session, 106 were ineligible after additional screening tests, 97 decided against participating, and 320 women were randomly assigned. Nine women were lost to follow-up after random assignment, and no adverse effects related to the intervention occurred. The primary analysis included 160 exercisers and 159 control participants. Recruitment began in May 2003 and was completed in June 2006, and 12-month follow-up of the study participants ended in July 2007. The two groups were similar at baseline with respect to demographic characteristics, body composition, and sex hormone concentrations (Table 1).

Table 2. Type of Physical Activity Recorded by Exercisers in the Daily Exercise Activity Logs

Recorded Activity	No. of Observations Recorded on the Exercise Log	%
At fitness facility		
Walking on treadmill	10,273	50.8
Bicycling	2,723	13.5
Elliptical trainer	2,480	12.3
Cross trainer	2,101	10.4
Walking on the track	2,093	10.3
Swimming	235	1.2
Calisthenics	62	0.3
Stationary rowing machine	71	0.4
Running	33	0.2
Rowing	32	0.2
Other	133	0.7
Total	20,237	
At home		
Walking	5,689	59.0
Walking on treadmill	870	9.0
Bicycling	717	7.4
Elliptical trainer	640	6.6
Cross trainer	295	3.1
Swimming	274	2.8
Running	105	1.1
Calisthenics	107	1.1
Stair climbing	89	0.9
Nordic skiing	63	0.7
Gardening	55	0.6
Curling	38	0.4
Golfing	31	0.3
Tennis	27	0.3
Rollerblading	20	0.2
Jogging	18	0.2
Skating	17	0.2
Other	522	5.4
Total	9,635	

Table 3. Physical Activity, Fitness, Dietary, and Weight Changes at 12 Months From Baseline by Group Assignment

Measure	No. of Exercisers	No. of Controls	Exercisers		Controls		Difference		*P*
			Mean	95% CI	Mean	95% CI	Mean	95% CI	
Total activity, h/wk	152	153	5.3	2.3 to 8.3	0.6	−3.6 to 4.8	4.7	−0.5 to 9.8	.075
Total activity, MET-h/wk	152	153	27.8	18.7 to 36.8	−0.2	−12.9 to 12.6	28.0	12.4 to 43.5	.001
Occupational activity, h/wk	152	153	1.2	−1.0 to 3.5	−0.5	−3.4 to 2.5	1.7	−2.0 to 5.4	.355
Occupational activity, MET-h/wk	152	153	4.6	−1.6 to 10.9	−1.5	−10.3 to 7.4	6.1	−4.7 to 16.9	.268
Household activity, h/wk	152	153	0.5	−1.4 to 2.3	−0.2	−2.7 to 2.4	0.7	−2.5 to 3.8	.679
Household activity, MET-h/wk	152	153	2.6	−2.5 to 7.8	−2.4	−9.9 to 5.2	5.0	−4.1 to 14.1	.282
Recreation activity, h/wk	152	153	3.5	2.8 to 4.1	1.2	0.4 to 1.9	2.3	1.3 to 3.3	< .001
Recreation activity, MET-h/wk	152	153	20.2	17.3 to 23.1	3.2	0.7 to 5.7	17.0	13.2 to 20.9	< .001
Maximal oxygen consumption, mL/kg/min	147	151	3.9	2.8 to 4.9	0.7	−0.2 to 1.6	3.2	1.7 to 4.6	< .001
Total energy intake, kcal/d*	150	153	−44.8	−107.4 to 17.8	−161.3	−225.3 to −97.3	116.5	27.4 to 205.7	.011
Body weight, kg	152	155	−2.3	−2.9 to −1.7	−0.5	−1.0 to 0.1	−1.8	−2.6 to −1.0	< .001

Abbreviation: MET, metabolic equivalent.
*Estimated from food frequency questionnaire.

Exercise Adherence

On their weekly logs, exercisers recorded a total of 29,872 individual exercise sessions noting 63 different activities (Table 2). At the fitness center, the most common activity was walking on the treadmill (51%), whereas for home-based activity, walking was the most frequent activity (59%). The exercisers recorded a mean of 3.6 sessions per week (SD = 1.3 sessions per week) for an average duration of 178.4 min/wk (SD = 76.1 min/wk). Objectively measured average heart rate was 80.1% (SD = 5.1%) of estimated heart rate maximum and 62.2% (SD = 9.8%) of estimated heart rate reserve. The average Borg Rating of Perceived Exertion reported was 12.7 ("somewhat hard" on the scale that ranges from 6 for "no exertion" to 20 for "maximal exertion"), and the average estimated energy expenditure was 5.7 metabolic equivalent-hours (MET-h) per session (SD = 0.7 MET-h per session).[37,38]

On the Past Year Total Physical Activity Questionnaire, exercisers reported a larger increase in recreational activity than controls (20.2 *v* 3.2 MET-h/wk, respectively; $P < .0001$; Table 3). Among the

Table 4. Differences in Sex Hormone Concentrations Between Exercisers and Controls at Baseline and the 6- and 12-Month Follow-Ups

Hormone	Baseline		6 Months		12 Months		Treatment Effect		Between-Group *P*
	Geometric Mean	95% CI	Geometric Mean	95% CI	Geometric Mean	(95% CI)	Ratio of Exercise/Control*	95% CI	
Estradiol, pg/mL									.004
Exercisers†	10.1	9.3 to 10.9	9.4	8.7 to 10.1	8.7	8.2 to 9.3	0.93	0.88 to 0.98	
Controls‡	10.2	9.4 to 11.1	10.0	9.3 to 10.8	9.9	9.1 to 10.7			
Estrone, pg/mL									.569
Exercisers	31.4	29.2 to 33.7	31.3	29.3 to 33.5	29.4	27.6 to 31.4	0.99	0.94 to 1.03	
Controls	31.3	29.1 to 33.7	31.2	29.0 to 33.5	30.6	28.5 to 32.9			
SHBG, nmol/L									.001
Exercisers	40.3	37.5 to 43.4	43.1	40.2 to 46.3	41.9	38.9 to 45.1	1.04	1.02 to 1.07	
Controls	38.1	35.7 to 40.8	39.2	36.7 to 41.9	38.4	35.9 to 41.1			
Free estradiol, pg/mL									.001
Exercisers	0.24	0.22 to 0.26	0.22	0.20 to 0.24	0.21	0.19 to 0.22	0.91	0.87 to 0.96	
Controls	0.25	0.23 to 0.27	0.24	0.22 to 0.26	0.24	0.22 to 0.26			
Androstenedione, pg/mL									.334
Exercisers	578	539 to 621	566	527 to 607	572.0	537 to 610	0.98	0.93 to 1.03	
Controls	553	514 to 595	560	520 to 604	577.3	534 to 624			
Testosterone, ng/dL									.620
Exercisers	23.9	22.3 to 25.8	23.7	21.9 to 25.6	23.4	21.7 to 25.3	0.99	0.95 to 1.03	
Controls	23.1	21.3 to 25.1	23.1	21.2 to 25.1	23.7	21.8 to 25.7			
Free testosterone, ng/dL									.094
Exercisers	0.35	0.32 to 0.38	0.33	0.30 to 0.36	0.33	0.31 to 0.36	0.96	0.92 to 1.01	
Controls	0.35	0.32 to 0.38	0.34	0.31 to 0.37	0.35	0.33 to 0.39			

Abbreviation: SHBG, sex hormone–binding globulin.
*The geometric mean ratios were estimated from least square means for the difference in treatment effect between exercisers and controls averaged across the entire study period adjusted for the baseline values and then back log-transformed.
†Exercise group: baseline, n = 160; 6 months, n = 154; 12 months, n = 154.
‡Control group: baseline, n = 159; 6 months, n = 153; 12 months, n = 155.

control group, 16 participants (10%) reported increasing their level of recreational activity by ≥ 20 MET-h/wk (200 min/wk of activity at ≥ 6 MET). Increases in physical fitness, as measured by estimated maximal oxygen consumption, were also significantly greater in exercisers than controls (3.9 *v* 0.7 mL/kg/min, respectively; $P < .001$). Energy intake decreased among controls by an average 161 kcal/d, whereas in exercisers, it decreased an average of 45 kcal/d ($P = .01$). Exercisers also lost −1.8 kg ($P < .001$) more body weight than controls.

Estrogen and Androgen Outcomes

The reduction in estradiol concentrations at 12 months was greater among exercisers than controls ($P = .004$; Table 4). Estrone changes were no different between exercisers and controls at 12 months ($P = .57$). An effect of exercise on SHBG levels ($P = .001$) and free estradiol levels ($P = .001$) was also observed.

Exercise adherence was not consistently associated with monotonic reductions in estradiol or estrone concentrations (Table 5). However, exercisers who adhered to 150 to 225 min/wk had an 18% reduction in estradiol concentrations compared with controls ($P = .002$), and a trend of percent change in estradiol levels with increasing exercise adherence was observed ($P = .005$). Similar results were found for free estradiol levels. A linear trend of increasing SHBG levels with decreasing exercise adherence was found ($P = .01$). Greater increases in SHBG levels were observed among exercisers who adhered to 150 to 225 min/wk (4.8%; $P = .035$) or more than 225 min/wk (5.3%; $P = .030$) compared with controls (−0.2%). After

Table 5. Hormone Concentrations at Baseline and 12 Months in Controls and Exercisers by Three Adherence Levels

Hormone	Baseline		12 Months		Ratio of 12 Months/Baseline*		% Change†	*P*‡	*P* for Trend§
	Geometric Mean	95% CI	Geometric Mean	95% CI	Mean	95% CI			
Estradiol, pg/mL									
Controls	10.3	9.5 to 11.2	9.9	9.1 to 10.7	0.96	0.91 to 1.01	−4.4	Reference	.005
Exercisers (< 150 min/wk)	10.1	8.7 to 11.7	9.6	8.4 to 10.9	0.95	0.87 to 1.03	−5.3	.778	
Exercisers (150-225 min/wk)	10.6	9.3 to 12.0	8.6	7.8 to 9.6	0.82	0.73 to 0.91	−18.2	.002	
Exercisers (> 225 min/wk)	8.9	7.9 to 10.0	8.2	7.3 to 9.2	0.92	0.85 to 1.00	−8.1	.128	
Estrone, pg/mL									
Controls	31.5	29.3 to 34.0	30.6	28.5 to 32.9	0.97	0.92 to 1.02	−2.9	Reference	.366
Exercisers (< 150 min/wk)	30.6	26.0 to 36.0	29.0	25.2 to 33.5	0.95	0.87 to 1.04	−5.2	.549	
Exercisers (150-225 min/wk)	31.2	28.2 to 34.6	29.9	27.2 to 32.9	0.96	0.87 to 1.05	−4.2	.721	
Exercisers (> 225 min/wk)	31.3	27.6 to 35.5	29.0	25.8 to 32.7	0.93	0.86 to 1.00	−7.1	.337	
SHBG, nmol/L									
Controls	38.5	36.0 to 41.2	38.4	35.9 to 41.1	1.00	0.97 to 1.02	−0.2	Reference	.010
Exercisers (< 150 min/wk)	38.6	33.3 to 44.8	37.9	32.7 to 44.0	0.98	0.93 to 1.04	−1.9	.574	
Exercisers (150-225 min/wk)	41.4	37.0 to 46.4	43.4	38.5 to 49.0	1.05	1.00 to 1.09	4.8	.035	
Exercisers (> 225 min/wk)	41.1	36.0 to 46.9	43.3	38.3 to 48.9	1.05	1.00 to 1.11	5.3	.030	
Free estradiol, pg/mL									
Controls	0.25	0.23 to 0.27	0.24	0.22 to 0.26	0.96	0.91 to 1.01	−4.4	Reference	.001
Exercisers (< 150 min/wk)	0.24	0.21 to 0.29	0.23	0.20 to 0.27	0.95	0.87 to 1.04	−4.8	.857	
Exercisers (150-225 min/wk)	0.25	0.22 to 0.29	0.20	0.18 to 0.23	0.80	0.72 to 0.89	−19.7	< .001	
Exercisers (> 225 min/wk)	0.21	0.18 to 0.24	0.19	0.17 to 0.22	0.91	0.83 to 0.99	−9.4	.078	
Androstenedione, pg/mL									
Controls	556	517 to 599	577	534 to 623	1.04	0.98 to 1.10	3.7	Reference	.602
Exercisers (< 150 min/wk)	588	501 to 689	548	477 to 630	0.93	0.85 to 1.03	−6.7	.116	
Exercisers (150-225 min/wk)	583	525 to 648	599	546 to 656	1.03	0.94 to 1.12	2.7	.927	
Exercisers (> 225 min/wk)	557	489 to 634	554	493 to 624	1.00	0.90 to 1.11	−0.5	.466	
Testosterone, ng/dL									
Controls	23.5	21.7 to 25.4	23.7	21.8 to 25.7	1.01	0.97 to 1.05	0.8	Reference	.549
Exercisers (< 150 min/wk)	23.6	20.3 to 27.5	22.7	19.3 to 26.7	0.96	0.89 to 1.03	−3.9	.274	
Exercisers (150-225 min/wk)	24.5	21.9 to 27.4	24.7	21.9 to 27.8	1.01	0.93 to 1.09	1.0	.876	
Exercisers (> 225 min/wk)	22.9	20.0 to 26.3	22.3	19.4 to 25.7	0.97	0.91 to 1.04	−2.7	.351	
Free testosterone, ng/dL									
Controls	0.35	0.32 to 0.38	0.35	0.33 to 0.39	1.01	0.97 to 1.05	0.9	Reference	.112
Exercisers (< 150 min/wk)	0.35	0.30 to 0.42	0.34	0.29 to 0.40	0.97	0.90 to 1.05	−2.9	.379	
Exercisers (150-225 min/wk)	0.35	0.31 to 0.39	0.34	0.30 to 0.39	0.98	0.89 to 1.07	−2.2	.446	
Exercisers (> 225 min/wk)	0.33	0.28 to 0.38	0.31	0.27 to 0.36	0.95	0.88 to 1.01	−5.4	.088	

NOTE. Controls, n = 155; exercisers (< 150 min/wk), n = 40; exercisers (150-225 min/wk), n = 67; and exercisers (> 225 min/wk), n = 47.
Abbreviation: SHBG, sex hormone–binding globulin.
*Ratio of geometric means at 12 months to geometric means at baseline.
†Percent hormone change at 12 months from baseline for that group.
‡*P* values for hormone change at 12 months from baseline between controls and the level of exercise adherence group adjusted for the baseline value.
§Trend analysis for hormone change at 12 months from baseline between controls and three adherence groups adjusted for the baseline value.

adjustment for weight change at 12 months, the intervention effect remained significant for estradiol ($P = .01$) and free estradiol ($P = .006$), whereas the SHBG results became nonsignificant ($P = .29$; Table 6).

No significant differences in the change in androstenedione or testosterone concentrations were observed between exercisers and controls at 6 and 12 months of follow-up (Table 4). Furthermore, changes in these hormone concentrations did not differ by exercise adherence (Table 5). There was a slight indication of a greater decrease in free testosterone among exercisers who exercised more than 225 min/wk (−5.4% change, $P = .088$); however, across the levels of adherence, there was no significant trend ($P = .112$).

DISCUSSION

This year-long aerobic exercise intervention program among postmenopausal sedentary women resulted in reductions in estradiol and free estradiol concentrations and increases in SHBG concentration that are consistent with a reduced risk of breast cancer. Although estrone concentrations also decreased in exercisers to a greater extent than in controls, the difference between groups did not achieve statistical significance. Likewise, changes in testosterone, androstenedione, and free testosterone levels were not significantly different between exercisers and controls. Greater adherence to the exercise intervention was also associated with greater decreases in estradiol concentration and increases in SHBG concentration. Finally, this study demonstrated that long-term adherence to a combination facility- and home-based exercise program is feasible and achievable for some women.

Table 6. Treatment Effect Ratio of Exercisers to Controls on Sex Hormone Concentrations Between Baseline and 12 Months Before and After Adjustment for Change in Body Weight

Hormone	Treatment Effect Ratio of Exercisers/Controls*	95% CI	*P*
Estradiol			
No adjustment for weight change	0.93	0.88 to 0.98	.004
Adjustment for weight change	0.94	0.89 to 0.99	.014
Estrone			
No adjustment for weight change	0.99	0.94 to 1.03	.569
Adjustment for weight change	0.99	0.94 to 1.04	.637
SHBG			
No adjustment for weight change	1.04	1.02 to 1.07	.001
Adjustment for weight change	1.01	0.99 to 1.04	.288
Free estradiol			
No adjustment for weight change	0.91	0.87 to 0.96	.001
Adjustment for weight change	0.93	0.88 to 0.98	.006
Androstenedione			
No adjustment for weight change	0.98	0.93 to 1.03	.334
Adjustment for weight change	0.98	0.93 to 1.03	.384
Testosterone			
No adjustment for weight change	0.99	0.95 to 1.03	.620
Adjustment for weight change	1.00	0.95 to 1.04	.889
Free testosterone			
No adjustment for weight change	0.96	0.92 to 1.01	.094
Adjustment for weight change	0.99	0.94 to 1.03	.554

Abbreviation: SHBG, sex hormone–binding globulin.
*The geometric mean ratios were estimated from least square means for the difference in treatment effect between exercisers and controls averaged across the entire study period adjusted for the baseline values and then back log-transformed.

This study found stronger effects on endogenous estrogen levels than the two other published exercise trials.[14,19] In the first study,[14] a statistically significant effect of exercise on estrogen levels was observed at 3 months but not at 12 months. The second trial found no significant effects of exercise on estrogen levels.[19] Our trial and the previous ones[15,19] observed no impact of exercise on androgen levels overall, but in the second trial, androgen levels decreased significantly in the exercise group who lost more than 2% body fat.[19] This study's results are consistent with some,[12,13,18,22] but not all,[21,39] observational studies that have found an association between physical activity and estrogen levels. The lack of effect of exercise on estrone levels found in our study may have occurred because estrone is rapidly converted to estrone sulfate and estrone levels in postmenopausal women are low, making changes in levels difficult to detect.

Physical activity may influence circulating estrogens by reducing adiposity, which decreases conversion of androgens to estrogens by aromatase.[5] In the current study, additional adjustment for weight change during the intervention attenuated the effect of the exercise intervention on SHBG but not estradiol or free estradiol. Physical activity may have effects independent of a change in adiposity, including a reduction in insulin levels, which, in turn, increases SHBG levels and decreases estradiol bioavailability.[5]

Recent guidelines recommend that adults perform at least 150 min/wk of moderate-intensity or 75 min/wk of vigorous-intensity aerobic physical activity.[35,36] This study provides evidence that circulating estrogens can be reduced and SHBG concentrations increased in women exercising 150 to 225 min/wk. The clinical significance of these findings can be evaluated by noting that the 1.2-pg/mL decrease in estradiol levels in this study was one fifth of the interquartile range (7 to 14 pg/mL) at baseline. Given that a large pooled analysis of prospective cohort studies[12] found that a doubling of estradiol levels in postmenopausal women is associated with a 29% (95% CI, 15% to 44%) increase in breast cancer risk, the impact of our intervention on estradiol levels would translate into a small breast cancer risk reduction. Further decreases in estradiol may occur with continued exercise.

This trial's strengths include the large sample size, a full year of supervised exercise intervention, low dropout rate, excellent adherence to the intervention, and the valid measures of estrogens and androgens. One limitation is the lack of compliance among 10% of controls who increased their vigorous recreational activity levels by $\geq$ 200 min/wk. A second limitation is the select sample of women who participated in the trial. The Alberta Physical Activity and Breast Cancer Prevention Trial was conducted as an efficacy trial in a select population to add information about the mechanisms by which physical activity may lead to a reduction in the risk of breast cancer. It is unclear what percentage of women would be able to adopt and maintain such an exercise program over an extended time period. Subsequent pragmatic behavioral trials are needed to determine the best strategies for increasing physical activity in the general population of women at higher risk of breast cancer.

In conclusion, this trial provides new evidence that previously sedentary, mostly overweight, postmenopausal women can achieve and sustain high levels of aerobic exercise that result in statistically significant changes in estradiol and SHBG concentrations that are

consistent with a reduced risk of postmenopausal breast cancer. Physical activity may offer an acceptable means of reducing breast cancer risk for postmenopausal women who are not at a high enough risk for the benefits to outweigh the adverse effects of chemoprevention options that are currently under investigation,[40-42] particularly given the broad health benefits associated with regular exercise.[35]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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