Effect of a 12-Month Randomized Clinical Trial of Exercise on Serum Prolactin Concentrations in Postmenopausal Women

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Abstract

Prolactin is associated with an increased risk of postmenopausal breast cancer; however, few modifiable factors are known to reduce prolactin concentrations. Therefore, we examined the effect of a 12-month moderate-intensity exercise intervention on serum prolactin concentrations as a secondary end point (primary end points were estrogens and androgens). We randomly assigned 173 postmenopausal women who were sedentary, overweight (body mass index >24 kg/m^2, body fat >33%), ages 50 to 75 years, and not using hormone therapy to an exercise intervention or stretching control group. The intervention was facility- and home-based (45 min, 5 days/wk moderate-intensity sports/recreational exercise). One hundred and seventy (98%) women completed the study. Prolactin concentrations were similar at baseline (P = 0.25, geometric mean exercisers = 6.9 and controls = 7.5 ng/mL). Overall, the intervention was not associated with changes in prolactin concentrations between exercisers and controls at 3 months (P = 0.46) or 12 months (P = 0.29). The intervention effect did not vary by baseline age, body mass index, parity, or change in percent body fat during the intervention. Among exercisers, there was a significant difference in prolactin concentrations by change in fitness (VO_2max) between baseline and 12 months. Exercisers whose VO_2max changed by <5% had a 5% increase in prolactin concentrations, whereas those who increased their VO_2max by 5% to 15% and >15% had a 11% (P = 0.03) and 7% (P = 0.01) decrease in prolactin concentrations, respectively. Although the exercise intervention had little effect on prolactin concentrations overall, increasing physical fitness was associated with reduced prolactin concentrations among postmenopausal women. (Cancer Epidemiol Biomarkers Prev 2007;16(5):895–9)

Introduction

Prolactin is a risk factor for breast cancer in both premenopausal and postmenopausal women (1-5), and experimental data suggests that prolactin promotes cell proliferation, alters cell motility, and increases tumor vascularization (4). However, few modifiable risk factors are known to alter circulating prolactin concentrations (4, 6). Physical activity reduces circulating sex hormone levels in postmenopausal women (7, 8), and thus, could plausibly modify prolactin concentrations.

In most (9-12), but not all (13), studies among young athletic individuals, physical activity acutely increased prolactin concentrations, although levels returned to basal concentrations within 12 to 24 h (9). In two studies, prolactin concentrations increased when participants completed a maximal exercise test, but not when completing a submaximal test (10, 14). Two studies have examined postmenopausal women, and both reported that intense acute exercise increased prolactin concentrations (15, 16). To our knowledge, however, no data are available concerning the relation between long-term physical activity and prolactin levels, particularly in postmenopausal women who are at high risk for breast cancer.

Therefore, we conducted a randomized controlled trial to assess the effect of a 12-month moderate-intensity exercise intervention on circulating concentrations of serum prolactin, as a secondary end point, among sedentary, overweight postmenopausal women not taking menopausal hormone therapy. The primary end points of the trial were looking at changes in serum estrogen and androgen concentrations. We also conducted a priori analyses to assess the effect of exercise on prolactin concentrations by change in body fat and, among exercisers, by adherence and changes in fitness.

Materials and Methods

This study was a randomized clinical trial comparing the effect of a 12-month moderate-intensity aerobic exercise intervention versus control on circulating prolactin concentrations measured at baseline (prerandomization) and at 3 and 12 months (17). All study procedures, including written informed consent, were reviewed and approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Participants. Participants were aged 50 to 75 years, lived in the greater Seattle area, were sedentary [<60 min/wk of moderate- or vigorous-intensity recreational activity and a maximal oxygen consumption (VO_2max) <25.0 mL/kg/min], had a body mass index (BMI) of ≥25.0 kg/m^2 (or BMI of 24.0-24.9 kg/m^2 and percent body fat measured by bioelectrical impedance >33.0%), were without serious comorbidities including diabetes, not taking menopausal hormone therapy in any form during the past 6 months, and were nonsmokers. We defined ''postmenopausal'' as having no menstrual period for the previous 12 months and, for women ages 50 to 54 years, serum follicle-stimulating hormone levels of >30 mIU/mL. Women were recruited through a combination of mass mailings and media placements (18). We randomly assigned

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173 women to an exercise intervention (n = 87) or a control group (n = 86), stratifying by BMI (<27.5 versus >27.5 kg/m^2).

Exercise Intervention. The exercise prescription consisted of at least 45 min of moderate-intensity exercise, 5 days per week for 12 months, and has been previously described in detail (19). Briefly, participants exercised for three sessions per week at a supervised study facility and 2 days/wk at home during months 1 to 3. During months 4 to 12, they attended at least one session per week at a study facility and exercised 4 days/wk at home or at the facility. Participants primarily engaged in treadmill and outdoor walking or stationary bicycling.

Women randomized to the control group attended weekly 45-min stretching sessions, and were asked not to change other exercise habits during the study. Exercisers and control participants were asked to maintain their usual diet.

We used two measures of exercise adherence. We assessed baseline and 12-month VO_2max in all participants using a maximal-graded treadmill test, with heart rate and oxygen uptake monitored by an automated metabolic cart (Medgraphics; ref. 19). In addition, exercise intervention participants kept daily activity logs of all sports or recreational activities. They recorded the type of exercise, peak heart rate, and duration of exercise. Activities completed at the facility were directly verified by exercise specialists on the activity log; all logs were reviewed, collected, and data entered weekly.

Baseline, 3-, and 12-Month Follow-up Measures. At baseline, 3, and 12 months for both exercisers and controls, we collected demographic information, medical history, health habits, medication use (including antidepressant medication), reproductive and body weight history, and physical activity (19). We also measured weight, height, and waist and hip circumferences. In addition, participants provided a 50 mL sample of blood. Participants were asked to refrain from the following before blood draw: exercise for 24 h, alcohol for 48 h, and food and drink other than water for 12 h. Blood was processed within 1 h of collection and serum was aliquoted into 1.8 mL tubes and stored at −70°C. Total body fat and percent body fat were assessed using a DXA whole-body scanner (Hologic QDR 1500; Hologic, Inc.) at baseline and 12 months.

Hormone Assays. Laboratory assays were done at the Reproductive Endocrine Research Laboratory (University of Southern California, F. Stanczyk) in November 2005. Prolactin was quantified by a chemiluminescent immunometric assay using the Immulite analyzer (Diagnostic Products Corporation). Samples were placed into batches such that, within each batch, all samples from a subject were included, the number of exercise and control subjects was approximately equal, the randomization dates of subjects were similar, and the sample order was random. Laboratory personnel were blinded to sample identities. Two specimens of a quality control pooled sample were placed in each batch. The intraassay and interassay coefficients of variation were both 2.9%.

Statistical Analyses. For our primary analysis, we compared the mean change in geometric mean prolactin concentrations from baseline to 3 and 12 months among exercisers and controls. The primary trial analysis assessed the intervention effect based on assigned treatment at the time of randomization, regardless of adherence or compliance status (intent to treat). One woman with no prolactin values at baseline was excluded; additional women missing prolactin measures at 3 or 12 months (n = 2 and 3, respectively) were excluded at that time point only. The analysis considered log-transformed prolactin measures, to correct for skewness in the data, at baseline, 3 months, and 12 months as repeated measures and assessed the intervention effects using a generalized estimating equation modification of the linear regression model (20). In secondary, a priori analyses, we assessed effect modification by baseline age, BMI, parity, and change in percent body fat over the trial. Among exercisers, we examined change in prolactin concentrations by the number of minutes exercised per week and change in VO_2max. In a secondary analysis, we excluded 24 women who used any type of antidepressant medications at any time point because they could alter prolactin concentrations (6). All statistical tests were two-sided. Statistical analyses were done using SAS software (version 8.2; SAS Institute, Inc.).

Results

After excluding women with a serum volume too low to conduct the prolactin assay, there were 172 women with prolactin measurements at baseline, 170 women at 3 months, and 169 women at 12 months. Participants were, on average, 61 years old with a mean BMI >30 for both exercisers and controls (Table 1). The intervention and control groups were statistically similar on a number of factors, including prolactin concentrations, demographic characteristics, body composition, and fitness level at baseline (Tables 1 and 2).

Participant Retention and Exercise Adherence. Exercisers completed an average of 4.0 days/wk of moderate-intensity sports/recreational activity, for a total of 171 min/wk (goal = 225 min/wk; ref. 19). Six (8%) exercisers ''dropped out'' of the exercise intervention (all after 3 months); three of these women provided a 12-month blood sample and were included in the analyses. In the control group, six (7%) women reported an increase of at least 225 min/wk of moderate to vigorous sports/recreational activity at 12 months. On average, VO_2max increased from baseline to 12 months in exercisers by 12.7% and in controls by 0.8% (P < 0.0001).

Intervention Effect. Women in the exercise and control groups experienced statistically similar changes in prolactin concentrations from baseline to 3 and 12 months (P = 0.46 and 0.29, respectively; Table 2). Exercisers had a nonsignificant

Table 1. Baseline characteristics of randomized participants

	Exercisers (mean ± SD)	Controls (mean ± SD)
N	87	86
Age (y)	60.7 ± 6.7	60.6 ± 6.8
BMI (kg/m^2)	30.5 ± 4.1	30.5 ± 3.7
Body fat, DXA (%)	47.5 ± 4.8	47.4 ± 4.6
VO_2max (mL/kg/min)	20.0 ± 3.6	20.5 ± 3.0
Parity*	2.8 (1.3)	2.8 (1.3)
	N (%)	*N* (%)
Education (%)		
High school graduate	10 (12)	9 (10)
Some college	36 (41)	35 (41)
College graduate	5 (6)	10 (12)
Graduate degrees	36 (41)	32 (37)
Ethnicity (%)		
Non–Hispanic White	74 (86)	75 (87)
African American	4 (5)	3 (4)
Asian/Pacific Islander	6 (7)	3 (4)
Hispanic/Latino	0 (0)	2 (2)
American Indian	0 (0)	2 (2)
Other	2 (2)	1 (1)
Family history of breast cancer		
None	59 (68)	58 (67)
First degree	14 (16)	16 (19)
Second degree	13 (15)	11 (13)
Ever used hormone replacement therapy	35 (48)	38 (52)
Current use of antidepressant medication	10 (11.6)	9 (10.5)

NOTE: There were no statistically significant differences at baseline between intervention and control subjects for these variables.
*Among parous women.

Table 2. Baseline, 3-, and 12-mo prolactin geometric means by intervention group

	N	Prolactin (ng/mL), geometric mean (95% CI)	Change from baseline	Difference in change in exercise vs. control	*P**
Exercise group					
Baseline	86	6.90 (6.28-7.58)	—	—	0.25
3 mo	86	6.94 (6.39-7.54)	+0.04	−0.29	0.46
12 mo	84	6.70 (6.14-7.32)	−0.20	−0.50	0.29
Control group					
Baseline	86	7.47 (6.78-8.24)	—	—	—
3 mo	84	7.80 (7.11-8.55)	+0.33	—	—
12 mo	85	7.77 (7.12-8.48)	+0.30	—	—

*P value at baseline compares exercisers versus controls at baseline. P value at 3 and 12 mo compares change from baseline in exercisers versus controls.

2.9% decline in prolactin from baseline to 12 months, compared with a nonsignificant 4% increase in controls. The effect of the intervention did not differ by baseline age, BMI, or parity, or after excluding women using antidepressant medications (data not shown). In general, the effect of the intervention did not differ by change in percent body fat over the year (data not shown). However, among the 16 exercisers and 27 controls who showed increased percent body fat, the exercisers decreased prolactin concentrations by 8% and the controls increased by 12% between baseline and 3 months (P difference = 0.001); results were similar, although less statistically significant at 12 months.

Compared with controls, exercisers who increased in fitness (as measured by VO_2max) had significantly larger declines in prolactin concentrations over the year (P = 0.03 and 0.01 for exercisers who gained 5-15% or >15% in VO_2max, respectively; Table 3). Exercisers whose VO_2max changed by <5% had a 5% increase in prolactin concentrations, whereas those who increased their VO_2max by 5% to 15% and >15% had a 11% and 7% decrease in prolactin concentrations, respectively. The P for trend across changes in fitness among exercisers compared with controls was nearly statistically significant (P = 0.07). A similar trend was observed among controls, although only 7 of 86 control women increased their VO_2max by >15% (data not shown). Adjustment for age did not substantially alter the results (data not shown).

Among exercisers, prolactin was not statistically significantly associated with adherence to the exercise intervention, as assessed by the number of minutes per week of exercise reported on the daily activity logs (Table 4). Women with intermediate adherence to the exercise intervention had the largest decline in prolactin concentrations over the year (−12%), compared to women with low adherence (+3%) and high adherence (+2%).

Discussion

Although prolactin is a risk factor for breast cancer (1-5), very few lifestyle factors are known to modify prolactin concentrations. Therefore, we examined whether a 12-month moderate- to vigorous-intensity exercise intervention was associated with changes in prolactin concentrations. Overall, we observed no clear association with the intervention, although in general, prolactin concentrations declined in exercisers and increased in controls. Among exercisers, we observed significant declines in prolactin concentrations over 1 year among women who increased their fitness level by >5%.

Previous studies have focused on the acute effects of exercise on prolactin concentrations. Most studies have reported a transient increase in prolactin directly following exercise, which returns to normal within 1 day (9-12, 14-16). This pattern has been observed in both fit and sedentary individuals (10, 13-16). Acute exercise exerts physical stress on the body, such as increasing heart rate and hypoxia (21), which can, in turn, increase prolactin levels. Specifically, increased prolactin during exercise may occur through several mechanisms including decreased hepatic and renal blood output (12), increasing core body temperature (22-24), or increasing lactate concentrations and hypoxia (14, 25, 26). The underlying biological pathways for these mechanisms are unclear, although the prolactin increase during exercise has been correlated to norepinephrine in one study (27) and ACTH in another (28). However, a third study reported that naltrexone, an opioid antagonist, did not alter the exercise-induced prolactin increase (29). To our knowledge, this is the first study to examine the effect of chronic exercise on prolactin concentrations. Reassuringly, prolactin levels were not increased by long-term physical activity in postmenopausal women.

Table 3. Baseline and 12-mo prolactin geometric means for exercisers, stratified by change in fitness as measured by VO_2max versus controls

	N	Prolactin (ng/mL), geometric mean (95% CI)	Change from baseline	*P**
Controls				
Baseline	86	7.47 (6.78-8.24)	—	—
12 mo	85	7.77 (7.12-8.48)	+0.30	Ref.
Exercisers				
Gained <5% VO_2max				
Baseline	23	6.64 (5.66-7.78)	—	—
12 mo	23	6.99 (6.14-7.96)	+0.35	0.96
Gained 5-15% VO_2max				
Baseline	23	6.99 (5.71-8.55)	—	—
12 mo	24	6.23 (5.35-7.26)	−0.76	0.03
Gained >15% VO_2max				
Baseline	28	6.86 (5.95-7.92)	—	—
12 mo	28	6.39 (5.32-7.66)	−0.47	0.01
P value for trend across change in fitness				0.07

*P value compares the change in prolactin concentrations between baseline and 12 mo among exercisers, stratified by change in fitness level, to the same change in controls.

Table 4. Baseline and 12-mo prolactin geometric means for exercisers by adherence (minutes per week of moderate to vigorous exercise)

	N	Prolactin (ng/mL), geometric mean (95% CI)	Change from baseline	*P**
<250 min/wk				
Baseline	29	7.00 (5.83-8.41)	—	—
12 mo	28	7.18 (6.07-8.48)	+0.18	Ref.
250-300 min/wk				
Baseline	30	6.93 (5.99-8.01)	—	—
12 mo	29	6.13 (5.54-6.78)	−0.80	0.69
>300 min/wk				
Baseline	27	6.76 (5.72, 7.97)	—	—
12 mo	27	6.87 (5.72-8.26)	+0.11	0.75

*P value compares the change in prolactin concentrations between baseline and 12 mo to the same change in women who exercised <250 min/wk.

We observed that prolactin concentrations decreased 7-11% over 12 months among women who increased their fitness levels. This decrease was similar among women who increased their fitness levels moderately (5-15% increase in VO_2max) or substantially (>15% increase in VO_2max), suggesting that any increase in fitness may lower prolactin concentrations. There was no significant correlation between VO_2max and prolactin (r = 0.09, P = 0.25) at baseline; however, because all the women were sedentary, the range of VO_2max levels was limited (range at baseline, 11.2-32.5 kg/m^2). Although no previous studies have examined long-term training effects on prolactin, a cross-sectional study of 21 men reported that chronic physical training seemed to have led to adaptive changes in prolactin secretion (14). Acute increases in prolactin concentrations were inversely related to the degree of training at certain absolute workloads, such that at a workload in which the prolactin response was maximal in untrained subjects, no response was registered in trained subjects. It is possible then, that increased fitness may not only change the acute prolactin response to the physical stress of exercise but may also lower basal levels (21). Thus, increasing fitness may lead to an adaptive response lowering circulating prolactin concentrations. This concept is supported by animal models reporting that constant exposure to a particular stressor could lead to lower prolactin concentrations over time (30). However, given the relative paucity of epidemiologic and experimental data, these potential biological mechanisms are only speculative.

Interestingly, we did not see an association with exercise adherence in the number of minutes per week. This may be because those who increased fitness exercised at a higher intensity or that changes in fitness reflect a measurable, phenotypic response to exercise initiation; the latter hypothesis suggests that women who were susceptible to increasing fitness with exercise were those who also had a change in prolactin concentrations. However, because this is the first study to examine these associations, the results should be interpreted with caution until this could be confirmed by other studies.

This study has several limitations. First, we assessed only one exercise intervention, thus we cannot make generalizations to other types, intensities, and durations of exercise. Second, adherence was lower during the second half of the study, even though overall adherence was high, such that we might not have been able to detect a more long-term difference in prolactin concentrations between exercisers and controls. Third, we did not intervene on diet in this study, therefore, we were not able to study the issues related to overall energy balance on prolactin concentrations. Finally, the population was restricted to postmenopausal, overweight, sedentary women; we cannot generalize these results to premenopausal women or lighter weight women. However, we had a large sample size and excellent measures of adherence.

Overall, we did not find that a long-term exercise intervention led to significant changes in prolactin concentrations compared with controls. However, increased fitness did seem to be associated with lower prolactin concentrations over the yearlong trial. This may reflect an adaptive response of prolactin to the physical stress of chronic exercise. Because this is the first study of the effects of long-term exercise on prolactin concentrations, these results need to be confirmed in future exercise intervention trials.

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