Research Article

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Effects of Aerobic Exercise on Premenopausal Sex Hormone Levels: Results of the WISER Study, a Randomized Clinical Trial in Healthy, Sedentary, Eumenorrheic Women

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Abstract

Background: It is hypothesized that exercise can lead to a decrease in breast cancer risk through several hormonal and nonhormonal mechanisms. The WISER (Women In Steady Exercise Research) study investigated the effects of aerobic exercise on premenopausal sex hormone levels.

Methods: Three hundred ninety-one sedentary, healthy, young eumenorrheic women were randomized either into an exercise intervention of 30 minutes of aerobic exercise 5 times a week for approximately 16 weeks ($n = 212$) or into a control group ($n = 179$). Serum levels of estradiol, estrone sulfate, testosterone, and sex hormone–binding globulin (SHBG), all in the midfollicular phase, and of progesterone, in the midluteal phase, were measured at baseline and at the end of the 16-week period.

Results: Compared with the controls ($n = 153$), exercisers ($n = 166$) experienced significant increases in aerobic fitness, lean body mass, and decreases in percent body fat. There were no significant changes in body weight and menstrual cycle length between or within groups. Progesterone decreased significantly in exercisers; however, this reduction was similar to that of the control group. No significant changes between or within groups were found for any of the other sex hormones or SHBG.

Conclusions: In premenopausal women, 16 weeks of 150 minutes per week of moderate aerobic exercise in young women did not significantly alter sex hormone or SHBG levels.

Impact: Any favorable effects that moderate aerobic exercise without an associated weight change may have on breast cancer risk in premenopausal women are unlikely to be a consequence of changes in levels of sex hormones or SHBG. *Cancer Epidemiol Biomarkers Prev; 20(6); 1098–106. ©2011 AACR.*

Introduction

Despite steady decreases in breast cancer mortality rates, breast cancer continues to be the most frequently diagnosed non–skin cancer and second leading cause of cancer death among women (1). Well-established risk factors for breast cancer include early age at menarche, late age at menopause and first childbirth, nulliparity, family history of breast cancer, benign breast disease, and nonreproductive factors such as hormone-replacement therapy use and physical inactivity (2, 3). Collectively, these factors increase the lifetime exposure of breast tissue to circulating sex hormones, which have been implicated, both experimentally and observationally, in the etiology of breast cancer.

In cultured mammary cancer cells, estrogen has been shown to promote cell proliferation (4, 5). Furthermore, although the role of progesterone in breast cancer is unclear, there is evidence that progesterone can potentiate the mitogenic effect of estradiol (6). Although not a steroid hormone, the glycoprotein sex hormone–binding globulin (SHBG) is also thought to play a role in breast carcinogenesis not only by regulating the bioavailability of estradiol and testosterone in circulation (7) but also by inhibiting estradiol-mediated cell growth and antiapoptosis in estrogen-dependent breast cancer cells (8).

In observational studies, elevated levels of circulating sex hormones are strongly associated with decreased risk for developing breast cancer. In a re-analysis of 13 prospective studies, postmenopausal women with the highest levels of estradiol, estrone, and testosterone had a 2-fold increase in breast cancer risk and those with

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the highest SHBG levels had a 34% decreased risk (9). Similarly, studies in premenopausal women have shown associations between increases in breast cancer risk with higher levels of estrogens and androgens and lower levels of progesterone and SHBG (10–21). Importantly, premenopausal levels of estradiol have been associated with postmenopausal breast cancer (16), suggesting exposures during this period may very well play a role in the initiation and promotion of breast cancer.

Physical activity is a modifiable lifestyle that has been associated with reductions in breast cancer risk of approximately 25% to 30% (22). Although many mechanisms have been suggested for the protective effect of exercise on breast cancer, reduction in circulating levels of sex steroid hormones is one factor that has been widely suggested (23). This has not been substantially studied in clinical trials, although in a recent, small clinical study of sedentary premenopausal women reported by Williams and colleagues (24), a 4-cycle intervention consisting of moderate-intensity aerobic exercise in combination with a caloric restrictive diet resulted in significant decreases in serum estradiol and urinary estrone-1-glucuronide (E1G) and pregnanediol glucoronide (PdG) levels. In contrast, our study, the Women In Steady Exercise Research (WISER) study, was a randomized trial of premenopausal women that investigated the effects of a moderate-to-vigorous exercise intervention independent of diet restriction and weight loss. We specifically sought to determine whether the exercise intervention would lead to alterations in levels of sex hormones and SHBG that would be consistent with a decreased risk of developing breast cancer.

Materials and Methods

The WISER study was a randomized, controlled, parallel-arm study that investigated the effects of a 16-week, moderate-to-vigorous intensity, aerobic exercise intervention on breast cancer biomarkers in young, healthy, sedentary, eumenorrheic women. The study was approved by the Human Subjects Review Committee at the University of Minnesota (Institutional Review Board ID 0505M69867). Written informed consent was obtained from each participant before participation. Details of the study design and methods have been described previously (25). Briefly, 391 non-smoking women aged 18 to 30 years residing in the Minneapolis-St. Paul metropolitan area with a body mass index (BMI) of 18 to 40 kg/m^2 (inclusive), having a self-reported menstrual cycle length of 24 to 35 days, and a sedentary lifestyle ($\leq$2 weekly sessions of moderate intensity exercise) were randomized into the WISER study. Exclusion criteria included use of hormonal contraceptives in the past 3 months of any form or depot-medroxyprogesterone acetate in the past 12 months, gynecologic problems, metabolic or endocrine-related diseases, non-melanoma cancer in the past 5 years, alcohol consumption of more than 7 servings per week, current or recent (past 6 months) pregnancy, and body weight changes greater than 10% over the past year. A total of 391 women started the study by completing baseline measurements during the luteal phase of menstrual cycle 1 and the follicular phase of cycle 2.

Randomization to either an exercise intervention or a no-exercise control group occurred after both baseline measurements were taken. Women with menstrual cycles averaging 25 to 31 days concluded the study with follow-up measurements during the luteal phase of cycle 5 and the follicular phase of cycle 6. Women with menstrual cycle lengths outside this range had follow-up measurements scheduled such that study duration after randomization was no less than 14 weeks and no more than 18 weeks. Specifically, women with menstrual cycle lengths of less than 25 days provided follow-up measurements during the luteal phase of menstrual cycle 6 and the follicular phase of cycle 7, whereas women with menstrual cycle lengths of more than 31 days completed these measurements during the follicular and luteal phases of cycle 5. Randomization was stratified on baseline BMI tertiles ($\leq$22.8, 22.8–26.3, $\geq$26.3) based on the 50th and 75th percentiles from NHANES I data and age (18–24 vs. 25–30). Initially, the randomization ratio (exercise/control) was 1:1 but due to the higher dropout rate in the treatment group, it was later changed to 60:40 to ensure that adequate sample size in both groups was achieved within the projected study timeline. Although failure to return for follow-up measurements resulted in being dropped out of the study, exercisers were additionally subject to study exclusion if they missed 15 or more exercise sessions. Figure 1 shows the screening, randomization, retention, and completion of WISER participants.

Exercise intervention

Women randomized to the exercise intervention trained aerobically 5 times a week for 30 minutes on a treadmill, stair-stepper, or elliptical machine, at a specified intensity based on age-predicted maximal heart rate (max HR) for 4 menstrual cycles (14–18 weeks). All training sessions took place at the University of Minnesota's Recreation Center. However, under special circumstances (housing relocation, time constrains, or traveling issues), participants were allowed to work out at another exercise facility. The exercise intensity was initially set at 65% to 70% of the age-predicted max HR and was gradually increased by 5% every 4 weeks until 80% to 85% of age-predicted max HR was reached (stage 1 = 65%–70%; stage 2 = 70%–75%; stage 3 = 75%–80%; stage 4 = 80%–85%). A certified personal trainer provided instruction on how to properly use the exercise machines and thoroughly complete an exercise log after each workout. Trainers supervised exercise sessions and reviewed the exercise logs at least once weekly to monitor adherence and safety. When not meeting with a trainer, participants were expected to complete the remaining of the workout sessions on their own at the specified training facility. Exercise adherence was monitored by a heart rate monitor (Polar Electro Inc.)

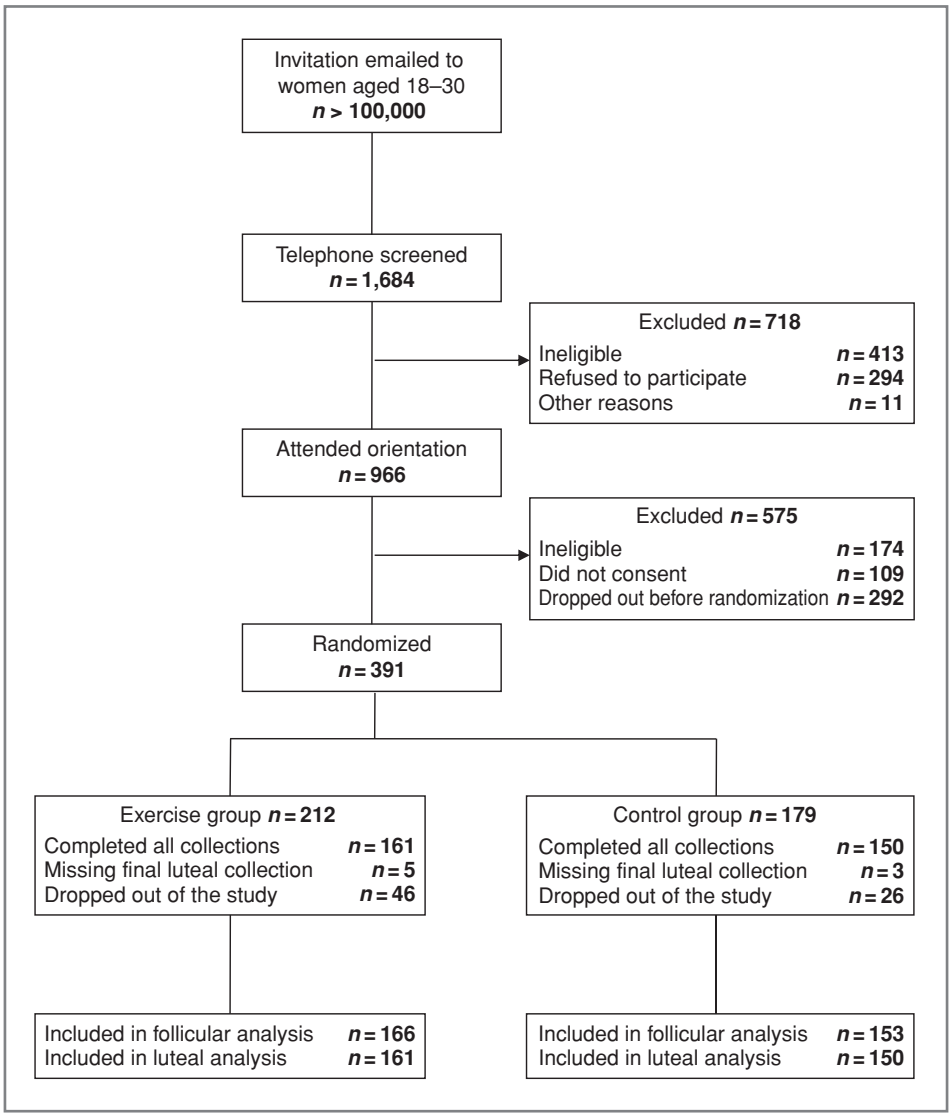

Figure 1. CONSORT diagram showing participant recruitment, screening, randomization, and retention.

and exercise logs. When the trainer detected a missed exercise session in the exercise logs, she contacted the participant to determine the reason for the missed session and to encourage compliance with the study protocol. Any physical activity carried out after randomization and outside the prescribed exercise intervention was assessed with a physical activity questionnaire by a research member at the end of the study.

All participants, regardless of randomization outcome, were advised to maintain their baseline body weight. Control participants were asked to maintain their usual level of physical activity and to not to change their eating habits. A thorough description of the exercise intervention has been described previously (25).

Outcome measures

All biological, anthropometric, and body composition measurements were taken at the General Clinical Research Center at the University of Minnesota. Body weight was measured 4 times during the study (baseline, cycle 3, cycle 4, and at follow-up) to the nearest 0.1 kg, using an electronic scale (Scale Tronix). Height was measured by a stadiometer at baseline without shoes to the nearest 0.1 cm (Scale Tronix). BMI was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). Body composition was assessed at baseline and follow-up luteal phase clinic visits by dual energy X-ray absorptiometry (DXA), using a Lunar Prodigy DXA apparatus (Lunar Radiation Corp.).

A submaximal treadmill test was used to assess aerobic fitness at baseline and immediately after the intervention. This workload was then converted to metabolic equivalents (MET) by using a standard conversion formula (26). Details of the fitness protocol have been described previously (25). Self-reported physical activity carried out a year before the study and during the 4-month follow-up period was assessed by research staff via a modified version of the Modifiable Activity Questionnaire (27).

This information was transformed into MET-hours per week (MET-h/wk) by using commonly accepted MET values (28). Dietary intake was assessed through self-reported, 3-day food records at baseline and follow-up. Nutrient intake was determined using The Food Processor SQL by ESHA Research.

Timing and occurrence of ovulation were assessed using a commercial 9-day Assure LH ovulation kit (Conception Technologies). This kit assesses for luteinizing hormone (LH) surge via ELISA, with a 96% accuracy rate with home use. For purposes of the study, day of ovulation was considered to be the day after a positive LH surge result. Participants were asked to inform research staff of positive LH surge results each month either by email or by phone.

Hormone and SHBG analyses

Blood samples were drawn between 6:45 and 11:00 AM after an overnight fast, centrifuged for 15 minutes (4°C at 1,000 × *g*), serum was separated, aliquoted, and stored frozen at −70°C. Baseline and follow-up blood draws took place during specific days of the menstrual cycles. Midluteal phase blood draws were scheduled 6 to 9 days after ovulation for analysis of progesterone during cycles 1 and 5 (cycle 6 for women with menstrual cycle lengths of <25 days), whereas midfollicular phase blood draws were on cycle days 7 to 10 for the analysis of all other sex hormones and SHBG during cycles 2 and 6 (cycle 5 and cycle 7 for women with menstrual cycle lengths of <25 days and >31 days, respectively).

Serum concentrations of estradiol, estrone sulfate, testosterone, progesterone, and SHBG were measured by laboratory personnel blinded to the intervention status. Commercially available RIA kits (Diagnostic System Laboratories) were used to measure estradiol (DSL-4400), estrone sulfate (DSL-5400), testosterone (DSL-4100), and progesterone (DSL-3900). An ELISA method (Immuno-Biological Laboratories-America) was used to measure SHBG (IBL-59106). Free and bioavailable fractions of estradiol and testosterone were calculated using the equations by Vermeulen and colleagues (29) and association constants estimated by the method of Mazer (30). Although not a sex hormone, SHBG will be referred to as such in the remainder of the text for ease of expression.

Samples were assayed in duplicate and in batches such that each batch contained both baseline and follow-up samples from each participant and an equal number of exercise and control participants. Two quality control blood samples were included in each batch. The mean intra-assay and interassay coefficients of variation were 5.7% and 16.6% for estradiol, 3.7% and 12.7% for estrone sulfate, 6.1% and 23.2% for testosterone, 8.6% and 11.7% for progesterone, and 4.9% and 5.2% for SHBG, respectively.

Statistical analysis

Unadjusted comparisons of baseline characteristics were done by using Student's *t* tests for continuous variables and χ^2 tests for categorical variables. Baseline associations between sex hormones and measures of body composition, adiposity, fitness, reproductive characteristics, and diet were determined using Spearman correlation coefficients. The main trial analysis assessed the intervention effect on hormones on an intent-to-treat basis such that all samples from participants who completed at least one follow-up blood measure were included in the analysis regardless of compliance level. Comparison of sex hormone levels at baseline, follow-up, and changes from baseline were adjusted for age and BMI strata with a general linear model. Baseline and follow-up analyses were conducted using log-transformed hormone values, whereas changes from baseline were analyzed on the original scale. Linear models were calculated using SAS software, version 9.2 (SAS institute Inc.). The value of $P < 0.05$ was considered statistically significant.

Results

Study participants

As shown in Figure 1, of the 212 and 179 women randomized into the exercise and control groups, 166 (78.3%) and 153 (85.5%), respectively, completed the WISER study ($P = 0.68$). With the exception of education level ($P = 0.10$), women who dropped out of the study were no different from women who completed the study in terms of age, height, weight, BMI, race, ethnicity, marital status, previous contraceptive use, and parity (data not shown). Both baseline and follow-up midfollicular and midluteal phase samples were obtained from 319 and 311 women, respectively. Most of the women who completed the study were single (82%), Caucasian (72%), educated (67% were at college level or higher), and had a normal BMI (63.5%). There were no significant differences in baseline demographic characteristics between the study groups (Table 1).

Baseline associations

At baseline, estradiol was significantly associated with assessed fitness ($r = -0.14$, $P = 0.01$). Testosterone was significantly correlated with age ($r = -0.15$, $P = 0.008$), BMI ($r = 0.13$, $P = 0.02$), and percent body fat ($r = 0.16$, $P = 0.005$). Progesterone was significantly associated with age ($r = 0.12$, $P = 0.03$). SHBG was positively associated with age ($r = 0.11$, $P = 0.05$) and negatively associated with BMI ($r = -0.22$, $P < 0.001$) and percent body fat ($r = -0.21$, $P = 0.001$). There were no significant associations between any of the sex hormones and self-reported physical activity, energy or alcohol intake, or reproductive factors such as age at menarche.

Treatment adherence

Adherence to the exercise intervention in the WISER study was excellent; on average, exercise participants completed 134 minutes per week of the assigned 150 minutes of exercise intervention. Exercise adherence in stage 1 was 97.6% and 85.3% in stage 4. More details about the exercise adherence can be found elsewhere (31).

Table 1. Baseline characteristics of randomized participants ($n = 319$) by treatment group

	Exercisers ($n = 166$)	Controls ($n = 153$)	*P*
Age, y	25.4 ± 3.4	25.2 ± 3.5	0.73
Height, cm	164.9 ± 6.9	165.4 ± 7.5	0.54
Weight, kg	67.4 ± 14.6	67.6 ± 14.6	0.94
BMI, kg/m^2	24.7 ± 4.7	24.7 ± 4.8	0.88
Fat mass, kg	24.2 ± 11.2	24.1 ± 10.6	0.90
% body fat	36.4 ± 8.8	36.1 ± 8.3	0.77
Lean mass, kg	39.7 ± 5.0	40.0 ± 5.2	0.63
Weight categories			0.38
Underweight (BMI < 18.5)	1 (1%)	1 (1%)	
Normal (18.5 ≤ BMI < 25)	100 (60%)	100 (65%)	
Overweight (25 ≤ BMI < 30)	46 (28%)	30 (20%)	
Obese (BMI > 30)	19 (11%)	22 (14%)	
Race			0.66
White	124 (75%)	107 (70%)	
Black	13 (8%)	12 (8%)	
Asian	20 (12%)	26 (17%)	
Other	9 (5%)	8 (5%)	
Hispanic	8 (5%)	6 (4%)	0.70
Education			0.66
High school or less	11 (7%)	7 (4%)	
Some college	43 (26%)	44 (29%)	
College graduate or more	112 (67%)	102 (67%)	
Marital status			0.89
Never married or partnered	138 (83%)	124 (81%)	
Married or partnered	25 (15%)	26 (17%)	
Separated or divorced	3 (2%)	3 (2%)	
Age at menarche,[a] y	12.8 ± 1.5	12.7 ± 1.3	0.53
Nulliparous	154 (93%)	144 (94%)	0.63
Previously using contraceptives	84 (51%)	82 (54%)	0.49
Family history of breast cancer[b]			0.60
No	129 (96%)	114 (97%)	
Yes	5 (4%)	3 (3%)	
Self-reported diet,[c] kcal/d	1,901 ± 420	1,933 ± 525	0.56
Self-reported physical activity, MET-h/wk	21.9 ± 16.6	21.8 ± 17.5	0.97
Assessed fitness (METs at 85% max HR)	6.9 ± 1.5	7.1 ± 1.5	0.45

NOTE: For continuous variables, values are mean ± SD, and *P* values are based on Student's *t* tests. For categorical variables, *P* values are based on χ^2 tests.

[a] $n = 310$.

[b] $n = 251$.

[c] $n = 312$.

Treatment effects

The exercise intervention resulted in a significant increase in aerobic fitness (increase of 0.90 METs reached at 85% of max HR for exercisers vs. 0.12 METs for controls) and improvements in body composition measures. Exercisers gained more lean mass (0.55 kg vs. 0.07 kg) and lost significantly more fat mass (0.57 kg vs. 0.04 kg) and body fat (0.95% vs. 0.09%) than controls. No changes in body weight were observed in either group (Table 2).

There were no differences between exercise and control groups in both baseline and follow-up sex hormone or SHBG levels, except that exercisers had significantly lower estrone sulfate levels, with and without adjustment for baseline levels (Table 3). Similarly, adjustment for baseline levels to changes from baseline comparisons in estrone sulfate resulted in similar means and *P* values as those obtained without the adjustment. Therefore, the results reported in Table 3 for follow-up and changes from baseline in estrone sulfate levels are

Table 2. Changes in fitness, body weight, body composition, and energy intake

	Baseline	Follow-up	Change from baseline
METs reached at 85% of max HR	$n = 319$	$n = 309$	$n = 309$
Exercise	7.0 ± 0.1	7.8 ± 0.1	0.90[a] ± 0.07
Control	7.0 ± 0.1	7.1 ± 0.1	0.12 ± 0.08
P	0.59	<0.0001	<0.0001
Weight, kg	$n = 319$	$n = 312$	$n = 312$
Exercise	68.0 ± 0.7	68.0 ± 0.7	−0.03 ± 0.2
Control	68.8 ± 0.8	69.0 ± 0.8	0.03 ± 0.2
P	0.41	0.37	0.83
BMI, kg/m^2	$n = 319$	$n = 312$	$n = 312$
Exercise	25.0 ± 0.2	25.0 ± 0.2	−0.01 ± 0.06
Control	25.2 ± 0.2	25.2 ± 0.2	0.01 ± 0.06
P	0.45	0.50	0.85
Fat mass, kg	$n = 319$	$n = 317$	$n = 317$
Exercise	24.6 ± 0.5	24.1 ± 0.5	−0.57[a] ± 0.1
Control	25.0 ± 0.5	25.0 ± 0.5	−0.04 ± 0.2
P	0.56	0.17	0.013
% body fat	$n = 319$	$n = 317$	$n = 317$
Exercise	36.9 ± 0.4	35.9 ± 0.4	−0.95[a] ± 0.2
Control	37.1 ± 0.4	37.0 ± 0.4	−0.09 ± 0.2
P	0.70	0.06	0.0003
Lean mass, kg	$n = 319$	$n = 317$	$n = 317$
Exercise	39.9 ± 0.4	40.4 ± 0.4	0.55[a] ± 0.1
Control	40.3 ± 0.4	40.4 ± 0.4	0.07 ± 0.1
P	0.41	0.93	0.003
Self-reported diet, kcal/d	$n = 312$	$n = 303$	$n = 298$
Exercise	1,898 ± 38	1,895 ± 51	−18 ± 51
Control	1,932 ± 40	1,711 ± 54	224[a] ± 53

NOTE: Values are means ± SE. Positive values represent increases from baseline, whereas negative values represent decreases from baseline.

[a]Significant within-group change from baseline ($P < 0.05$).

age- and BMI-adjusted only. With the exception of progesterone, there were no within-group differences in sex hormone or SHBG levels. Progesterone levels decreased modestly but significantly ($P = 0.02$) in exercisers; however, this reduction was statistically similar to that experienced by control participants. No differences were found between groups in changes from baseline in any of the sex hormone or SHBG levels. Results were consistent when comparisons were restricted to normal weight, overweight, and obese subgroups. There were no significant changes from baseline in menstrual cycle length between or within groups (data not shown).

Discussion

According to the American College of Sports Medicine and the American Heart Association, 30 minutes of moderate-intensity aerobic exercise carried out 5 times a week is consistent with the promotion and maintenance of health (32). The WISER study was the first randomized, controlled study designed to test whether a moderate-to-vigorous exercise regimen resulting in no weight loss would result in changes in circulating levels of blood sex hormones and SHBG associated with reduction of breast cancer risk in premenopausal women.

The exercise intervention in the WISER study resulted in favorable changes in aerobic fitness and body composition measures; however, no significant differences were observed between exercisers and control participants in the changes of serum estradiol, estrone sulfate, testosterone, progesterone, or SHBG levels. Although the study was not specifically powered to assess for hormonal differences between the 2 groups, the virtually identical results for these parameters make it unlikely that physiologically important differences were present. Most cross-sectional data are consistent with these null results. For example, previous studies have found no significant associations between physical activity and premenopausal levels of estrone sulfate (33), testosterone (34, 35), progesterone (34, 36), and SHBG (34, 36, 37). As for total

Table 3. Baseline, follow-up, and changes from baseline in sex hormone and SHBG levels

Sex hormone ($n = 319$)	Baseline	Follow-up	Change from baseline
Estradiol, pg/mL			
Exercisers	56 (50–63)	60 (56–64)	2.3 ± 2.8
Controls	58 (51–65)	62 (58–66)	1.4 ± 3.0
P	0.66	0.44	0.83
Bioavailable estradiol, pg/mL			
Exercisers	39 (36–41)	40 (37–43)	1.4 ± 1.9
Controls	41 (39–44)	43 (40–46)	1.1 ± 2.0
P	0.14	0.13	0.89
Free estradiol, pg/mL			
Exercisers	1.3 (1.2–1.4)	1.4 (1.3–1.4)	0.05 ± 0.06
Controls	1.4 (1.3–1.5)	1.5 (1.4–1.6)	0.04 ± 0.07
P	0.14	0.13	0.89
Estrone sulfate, ng/mL			
Exercisers	2.0 (1.8–2.2)	2.0 (1.9–2.2)	−0.04 ± 0.06
Controls	2.2 (2.0–2.4)	2.3 (2.1–2.4)	−0.01 ± 0.06
P	0.040	0.017	0.74
Testosterone, pg/mL			
Exercisers	451 (423–482)	446 (419–475)	−8.8 ± 9.0
Controls	473 (442–506)	464 (435–495)	−13.6 ± 9.5
P	0.32	0.38	0.71
Bioavailable testosterone, pg/mL			
Exercisers	204 (187–222)	204 (188–222)	−2.7 ± 5.6
Controls	224 (205–245)	225 (206–246)	−3.0 ± 5.8
P	0.13	0.11	0.97
Free testosterone, pg/mL			
Exercisers	8.8 (7.9–9.7)	8.7 (8.0–9.5)	−0.13 ± 0.25
Controls	9.2 (8.3–10.2)	9.6 (8.8–10.5)	−0.04 ± 0.30
P	0.50	0.11	0.80
Progesterone,[a] ng/mL			
Exercisers	12 (10–14)	10 (8–11)	−2.2[b] ± 0.9
Controls	13 (11–15)	12 (10–14)	−1.1 ± 1.0
P	0.61	0.12	0.42
SHBG, nmol/L Exercisers	27 (25–30)	26 (24–29)	−1.3 ± 1.0
Controls	25 (23–27)	24 (22–26)	−1.8 ± 1.1
P	0.15	0.08	0.74

NOTE: Values are age- and BMI-adjusted geometric means (95% CI) for baseline and follow-up, as well as mean ± SE for changes in hormone levels. Positive values represent increases from baseline, whereas negative values represent decreases from baseline.

[a] $n = 311$.

[b] Significant within-group change from baseline ($P < 0.05$).

and free estradiol, only 2 (36, 38) of 6 (33–38) and 1 (34) of 2 (33, 34) studies, respectively, have found a significant negative association. In contrast to our results, the one study that evaluated the association between physical activity and both estrone and free testosterone levels did find significant negative associations (34).

More importantly, our results are consistent with 3 small clinical studies in premenopausal women. In a study by Rogol and colleagues (39), there were no differences in integrated estradiol and progesterone levels in 17 subjects who completed 1 year of endurance training compared with 6 (nonrandomized) controls. In the

WISER pilot study, 15 weeks of moderate-to-vigorous intensity aerobic exercise in 15 sedentary premenopausal women resulted in no significant changes in urinary estradiol or estrone levels despite a significant, albeit small (1.2 kg), loss in weight (40). In the study of Williams and colleagues, sedentary premenopausal women allocated to 120 to 240 minutes per week of moderate exercise in combination with a caloric restrictive diet (20%–35% of baseline energy requirements) experienced significant reductions in body weight (3.7 kg), serum estradiol, and urinary E1G and PdG levels (24). However, the control participants, who followed an intervention comparable with that of the WISER exercisers (36 minutes of moderate exercise twice a week in addition to unrestrictive, eucaloric diet), did not experience significant changes in body weight or sex steroid levels.

There are different reasons why the exercise intervention of the WISER study may have failed to result in detectable changes in sex hormone and SHBG levels. It has been hypothesized that the effects of exercise on reproductive hormones are mediated by changes in body composition (22, 41). Although such changes are less important for cycling premenopausal women than for postmenopausal women, in whom the primary source of estrogens is peripheral aromatization of androgens in adipose tissue (42, 43), in our study the lack of any such effects may have been because body composition changes were modest. Thus, perhaps, a longer exercise intervention would have yielded different results. It is also possible that a more intensive sampling and/or sampling closer to the time of ovulation (when estradiol levels are higher) would have improved our ability to detect changes in hormone concentrations.

Alternatively, it is possible that exercise exerts an independent effect on hormone exposure by disrupting hypothalamic function resulting in changes in menstrual cycle characteristics such as delayed onset of menarche, irregular or absent menstrual periods, abnormal or loss of luteal function, and longer menstrual cycle length (22, 41). In our study, although we observed no significant within- or between-group changes in menstrual cycle length, it is possible that follicular and luteal phase lengths may have changed significantly even when no changes in menstrual cycle length were detected. We are currently investigating whether the WISER exercise intervention resulted in changes in follicular and luteal phase lengths as well as changes in estrogen metabolism. Finally, it is possible that exercise may decrease breast cancer risk in premenopausal women through nonhormonal mechanisms such as changes in endogenous oxidative stress, insulin and glucose metabolism, inflammatory marker levels, and immune function (22, 41). We plan to separately report the effects of the exercise intervention on biomarkers for these mechanisms.

The WISER study is the first clinical trial with randomized controls to study the effects of aerobic exercise on serum reproductive hormone levels in premenopausal women. Strengths include a large sample size, carefully timed follicular and luteal blood samples, and excellent protocol adherence. Findings from this study do not support the hypothesis that, at least in the absence of weight change or obvious menstrual cycle disruption, 150 minutes per week of moderate aerobic exercise leads to reductions in sex hormone concentrations and increases in SHBG concentrations in premenopausal women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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