Association of Physical Activity with Reproductive Hormones: The Penn Ovarian Aging Study

Kathryn H. Schmitz,[1] Hui Lin,[2] Mary D. Sammel,[1] Clarissa R. Gracia,[3] Deborah B. Nelson,[6] Shiv Kapoor,[4] Tracey L. DeBlasis,[2] and Ellen W. Freeman[3,5]

[1]Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, [2]Center for Research in Reproduction and Women's Health, [3]Department of Obstetrics/Gynecology, [4]General Clinical Research Center, and [5]Department of Psychiatry, University of Pennsylvania School of Medicine; and [6]Departments of Public Health and Obstetrics/Gynecology, Temple University College of Health Professions, Pennsylvania, Pennsylvania

Abstract

Background: **Physical activity is associated with reduced risk for breast cancer, perhaps through reductions in circulating reproductive hormones (estrogens and androgens). There may also be a role for physical activity in regulating menopausal symptoms. Few studies have examined associations of physical activity on hormone levels. None have examined the potential effect of the menopausal transition on the associations between physical activity and reproductive hormone levels.**

Materials and Methods: **Data from the Penn Ovarian Aging Study were used for this analysis. Self-reported physical activity was assessed in 391 women up to four times over 10 years and extending across the menopausal transition. Other assessments included reproductive hormones via RIA (estradiol, luteinizing hormone, follicle-stimulating hormone, testosterone, DHEA sulfate), body weight, and height. Multivariate repeated measures regression models were developed to compare reproductive hormone levels within physical activity tertiles, adjusting for age, follow-up time, smoking, and ethnicity.**

Results: **Activity level was inversely associated with estradiol in the subgroup in the late transition stage. Adjusted means for estradiol were 24.6 and 37.9, a relative difference of 54% in estradiol when comparing highest to lowest activity tertile ($P = 0.02$). Similarly, in this subgroup, there was an inverse association between physical activity and testosterone levels (means of 11.1 and 15.94 in the highest and lowest tertile, a 47% relative difference; $P = 0.01$). There were no significant associations of activity with any other reproductive hormone.**

Conclusions: **These results identify a particular window of the menopausal transition during which physical activity is associated with reduced estradiol and/or testosterone levels.** (Cancer Epidemiol Biomarkers Prev 2007;16(10):2042–7)

Introduction

Regular physical activity is associated with a decrease in risk of postmenopausal breast cancer (1). One of the proposed mechanisms for this association is a reduction in circulating levels of reproductive hormones, specifically estrogen and androgens, which are widely accepted to be etiologically linked to postmenopausal breast cancer (2-8), as well as endometrial (9) and ovarian cancer (10).

It is reasonable to hypothesize that premenopausal endogenous reproductive hormone exposure may be associated with risk for postmenopausal breast cancer and other hormonally related cancers by inducing increases in cellular proliferation rates in the breast and other reproductive tissues (2). However, there are important differences in the mechanisms by which reproductive hormones are formed in premenopausal versus postmenopausal women. Levels of circulating hormones in postmenopausal women are determined by adrenal activity and conversion of testosterone and androstenedione to estrone (11) in adipose tissue (12). Physical activity reduces body fat, and after the menopausal transition, body fat becomes important to determining endogenous estrogen and androgen levels. Physical activity has been shown to decrease estrogens and androgens in association with reduced body fat in postmenopausal women (13, 14).

Conversely, in premenopausal women, ovarian hormone production predominates, at least for estrogens, and circulating levels are less influenced by adipose tissue (15). The relative balance of ovarian versus adrenal production of androgens is as yet unclear (16), although there is evidence of significant testosterone production by the ovaries even after menopause (16). Physical activity may alter endogenous hormone exposure through differing mechanisms among premenopausal versus postmenopausal women. Furthermore, during the menopausal transition, there is a gradual shift away from the predominance of ovarian estrogen production.

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Requests for reprints: Kathryn H. Schmitz, Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, 423 Guardian Drive, 921 Blockley Hall, Philadelphia, PA 19104. Phone: 215-898-6604; Fax: 215-573-2265. E-mail: Schmitz@mail.med.upenn.edu

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Circulating reproductive hormone levels may be increasingly influenced by body fat as women progress through the menopausal transition. This may mean that physical activity, through alterations in body fat, may become increasingly important to determining circulating reproductive hormone levels across the menopausal transition. However, to our knowledge, there have been no studies that have examined whether the association of physical activity and endogenous reproductive hormones may change during the menopausal transition. If physical activity does influence endogenous reproductive hormones among perimenopausal women in a manner that would be consistent with reduction of breast cancer risk, this may represent a new window of opportunity for interventions.

In addition to breast cancer risk, serum levels of reproductive hormones have been observed to be associated with vasomotor symptoms among perimenopausal and postmenopausal women (17). More specifically, lower levels of estrogens and androgens have been found to be associated with higher vasomotor symptoms (17). Vasomotor symptoms are experienced by the majority of women as they traverse the menopausal transition (18) and are a common reason for seeking medical attention during this phase of life (19). Therefore, understanding the effect of physical activity on reproductive hormones during the menopausal transition may have importance for understanding the relationship of physical activity and menopausal symptoms, in addition to the physical activity–breast cancer relationship.

Few studies have directly examined the role of physical activity on hormones; none have examined the potential effect of the menopausal transition on these associations. In this report, we use data from the Penn Ovarian Aging Study to explore the potential for self-reported leisure time physical activity to influence circulating hormone levels across the menopausal transition. The *a priori* hypothesis of this analysis was that the inverse association of physical activity with circulating reproductive hormone levels would become increasingly apparent as women progressed through the menopausal transition stages, as the ovaries decreased production of these same hormones. Our hypotheses assume that body fat plays an increasing role in determining circulating reproductive hormones as women traverse the menopause and that physical activity will become increasingly associated with reproductive hormones across the menopausal transition for this reason. To more completely explore this hypothesis, we also undertake analyses to explore whether an observed association of physical activity and reproductive hormones might differ by body size.

Materials and Methods

Study Participants. The Penn Ovarian Aging Study was designed to examine the natural hormone profiles of women during the transition to menopause and to identify associations between hormonal changes and menopausal symptoms (20, 21). At study entry, participants were 35 to 47 years old, had normal length menstrual cycles over the past 3 months (22-35 days), had an intact uterus, and had at least one ovary. Exclusion criteria included current use of hormonal or psychotropic medications (including hormonal contraception or replacement), pregnancy or breast feeding, serious health problems associated with compromised ovarian function (e.g., diabetes, liver disease, breast or endometrial cancer), and alcohol or drug abuse during the past year. The study was approved by the University of Pennsylvania Institutional Review Board. Written consent was obtained.

Of the 436 subjects enrolled at baseline, 394 were evaluated in the second assessment period, which was the first observation where physical activity data were collected. The women in the present analyses contributed data from each time they attended an assessment (up to four assessments of physical activity), for a total of 1321 observations. Four participants had one or more observations censored because the participant was lactating or pregnant at the time of assessment. Data from 20 women were set to missing from the time point at which they reported having had a hysterectomy with bilateral oopherectomy. In addition, there were 38 women who had one or more observations censored due to hormone replacement therapy or a diagnosis of cancer.

Measures. Data for the present analyses include the four assessment periods at which physical activity data were collected: assessment periods 2, 6, 8, and 10 in the Penn Ovarian Aging Study. The second and sixth examinations were separated by 30 months. The sixth and eighth assessments were separated by 24 months; the eighth and tenth assessments were separated by 24 months. Each assessment period had two visits, scheduled during the follicular phase (days 1-6) of two consecutive menstrual cycles. If a woman did not menstruate within 2 months of being contacted for her assessment appointment, she was brought in for her first appointment and then her second appointment was ~1 month later. Each subject contributed up to eight blood samples for the hormone assays. The average of the two hormone assays per assessment period was used in the analysis.

Nonfasting blood samples were centrifuged and frozen in aliquots at −80°C. It has been observed that reproductive hormone secretion is similar in the fasted and nonfasted state (22). Assays were conducted at the General Clinical Research Center in batches that included four visits per subject to reduce the within-subject variability due to assay reagent kit differences. Estradiol, follicle-stimulating hormone, luteinizing hormone, total testosterone, and DHEA sulfate were measured by RIA using Coat-A-Count commercial kits (Diagnostic Products). Assays were done in duplicate for all hormones and repeated if values differed by >15%. Interassay and intraassay coefficients were ≤5%.

At each assessment, a trained research assistant administered a structured interview that included menstrual cycle dates, reproductive history, general health status, and smoking (current, past, or never). Demographic characteristics (e.g., age, ethnicity) were collected at baseline. Body mass index (BMI; kg/m^2) was calculated from the average of two measurements of weight and height at each assessment.

Menopausal status was determined at each assessment. The length of the current menstrual cycle was determined from the menstrual dates at each of the two study interviews in the assessment period (interviews

were conducted within first 6 days of bleeding). Confirmatory dates were obtained from the menstrual dates recorded in daily symptom diaries completed by subjects during each assessment period, the dates of the two previous menstrual periods obtained at each interview, and the date of the last menstrual period if none occurred within the assessment interval. The definitions of menstrual status were adapted from a consensus statement on a staging system for reproductive aging in women (23). At each assessment, women were assigned to one of five possible categories based on bleeding patterns during that period: premenopausal, regular menstrual cycles in the 22 to 35 day range; late premenopausal, change in cycle length ≥7 days in one menstrual cycle compared with the woman's personal baseline at enrollment in the cohort; early transition, change in cycle length ≥7 days from the women's personal baseline at enrollment in the cohort and observed for at least two cycles in the study; late transition, 3 to 11 months amenorrhea; postmenopausal, ≥12 months amenorrhea (no hysterectomy).

Physical activity was assessed using the Paffenbarger Physical Activity Survey (24). This survey has been shown to have excellent reliability and predictive validity (25). Kilocalories of leisure time physical activity per week were calculated (25) and categorized into data-driven tertiles for analysis. The median value in each tertile of 2,260, 957, and 392 kilocalories per week (kcal/wk) can be roughly translated into five sessions per week of walking 4.0 mph for 1.5 h, 38 min, and 16 min, respectively (26).

Statistical Analysis. The natural log of the hormone levels was used for all analyses to accommodate modeling assumptions. The group average log hormone levels have been back transformed and presented as geometric mean levels in tables. General linear mixed effects regression models for repeated measures were used to estimate the associations between hormones and physical activity tertiles adjusted for race, smoking, baseline age, and time on study. Adjustment variables were included to avoid possible confounding, as each of the variables included in our final models were observed to be associated with both physical activity and at least one of the hormones examined in bivariate analyses at a P value of 0.10 or lower (data not shown). The within-woman correlation of the repeated measurements was taken into account using generalized estimating equation adjustments (27). In addition to evaluating physical activity tertiles as a categorical variable, tests for a linear trend were conducted using an extension of the Cochran-Armatige test for trend. Additional models were developed to explore whether an observed associations of physical activity and reproductive hormones varied by BMI. These models included main effects for physical activity and BMI, as well as a cross-products term of a three-group BMI variable with the three group physical activity variable. These models, results of which are shown in Table 4, were not adjusted for covariates due to small sample sizes within each cell. All analyses were conducted using SAS version 9.1 (SAS Institute, Inc). A two-sided P value of <0.05 was considered statistically significant.

Results

The analyses presented herein represent data from 394 women who attended the second Penn Ovarian Aging Study examination and up to four subsequent assessments. Table 1 presents the number of women who contributed data to these analyses at each assessment period, along with their menopausal status at each assessment. For example, there were 123 observations used in the analyses for which the menopausal transition category was ''late transition,'' 4 at assessment 2, 13 at assessment 6, 46 at assessment 8, and 60 at assessment 10. Of the 394 women in the data set, 60% contributed data to all four time points included in this analysis, 17% contributed to three time points, 10% contributed to two time points, and 11% contributed to only one measurement time point.

Table 2 presents descriptive characteristics of all 394 women, who were evaluated at the first assessment used in the present analyses. The range of physical activity within the highest tertile was 1,454 to 25,596 kcal/wk, with a median of 2,260 kcal/wk. In the middle tertile, the range was 644 to 1,449 with a median of 957 kcal/wk. In the lowest tertile, the range was 0 to 643 kcal/wk with a median of 392 kcal/wk.

In unadjusted models and in the women in the late transition phase only, physical activity level was marginally inversely associated with estradiol (geometric means of 24.6, 27.1, and 38.0 in the highest, middle, and lowest tertiles, respectively; $P = 0.05$ comparing highest to lowest tertile; $P = 0.04$ in test for linear trend) and inversely associated with testosterone levels (geometric means of 4.2, 27.3, and 23.4 in the highest, middle and lowest tertiles, respectively; $P < 0.0001$ comparing highest to lowest tertile; $P < 0.0001$ in test for linear trend). Table 3 shows results from multivariate models adjusted for age, time on study, ethnicity, and smoking status. As with the bivariate models, significant inverse associations of physical activity tertiles with estradiol and testosterone were observed in the late transition phase only. Tests for

Table 1. Menopausal status at each assessment period

Assessment period	Menopausal status					
	Premenopause	Late premenopause	Early transmenopause	Late transmenopause	Postmenopause	Total
2	257	80	49	4	0	390*
6	188	59	71	13	11	342
8	118	26	83	46	26	299
10	98	18	51	60	63	290
Total	661	183	254	123	100	1321

*At period 2, two subjects were pregnant and two subjects had hysterectomies.

Table 2. Description of participants at baseline for this report (n = 394)

Categorical variable		n	%
Smoking	Yes	148	37.6
	No	246	62.4
Race	Caucasian	193	49.0
	African American	201	51.0
Physical activity*	Highest tertile (median = 2260 kcal/wk)	129	32.7
	Middle tertile (median = 957 kcal/wk)	131	33.3
	Lowest tertile (median = 392 kcal/wk)	120	30.5

Continuous variables	Mean	Min, max	SD
Age (y)	42	36, 50	3.5
Estradiol (pg/mL)	44.4	2.5, 247.5	29.3
Testosterone (ng/dL)	13.6	1.0, 243.7	15.9
Luteinizing hormone (mIU/mL)	3.7	0.6, 26.1	3.3
Follicle-stimulating hormone (mIU/mL)	8.9	1.9, 59.5	7.1
DHEA sulfate† (μg/dL)	103.8	7.1, 388.7	56.1

*There were 14 women who were missing physical activity data at the first assessment.
† Dehydroepiandrosterone sulfate.

linear trend revealed a marginally significant linear trend for the association of physical activity with estradiol (P = 0.05) and a statistically significant linear trend for the association of physical activity and testosterone (P < 0.01) in the late transition group only. Bivariate and multivariate analyses adjusted for ethnicity, smoking status, time on study, and baseline age, with up to four observations per person, indicated no association between physical activity and follicle-stimulating hormone, luteinizing hormone, or DHEA sulfate in any menopausal transition stage (results not shown).

We hypothesized that physical activity would be differentially important to reproductive hormone levels according to body size. In these data, we noted that the mean BMI level in the top, middle, and lowest tertiles of physical activity were 29.2, 29.6, and 30.1, respectively, with a P value of 0.0001 in a test for linear trend. We repeated several models that predicted estradiol and testosterone among women in the late transition period after adding BMI as a categorical variable (<25, 25-29.9, and ≥30 kg/m^2). Due to the limited sample size in this late transition subgroup, we were not able to adjust for other covariates in these models. Results are shown in Table 4.

Among the 92 women contributing 98 observations in the late transition phase, the terms in the regression models that were intended to assess modification of the effect of physical activity by BMI had P values of 0.06 and 0.0001 for models predicting estradiol and testosterone, respectively. The nature of the effect modification was such that differences in testosterone across physical activity tertiles were most evident in the women with a BMI of ≥30. The pattern of the effect modification was less clear for estradiol. The geometric mean for the estradiol level of women in the late transition period who were in the lowest physical activity tertile and who were in the 25 to 29.9 BMI category was 96.7 pg/mL. This value is clearly higher than all other values in the table, likely results from an unstable estimate given a sample size of five observations for that particular cell in Table 4.

Discussion

Physical activity of ≥1,454 kcal/wk was associated with 54% and 47% lower estradiol and testosterone levels, respectively, among women in the late transition phase

Table 3. Association of physical activity tertiles with estradiol and testosterone within menopausal transition categories

Physical activity tertiles	Top (≥1,454 kcal/wk)	Middle (644-1,449 kcal/wk)	Lowest (0-643 kcal/wk)
Estradiol (pg/mL), mean (95% confidence interval)			
Postmenopause	14.6 (11.0, 19.3)	15.7 (10.7, 23.0)	16.3 (11.8, 22.6)
Late transmenopause*	24.6 (17.8, 33.9)	10.6 (24.4, 38.5)	37.9 (29.4, 48.8)
Early transmenopause	37.6 (29.6, 47.8)	34.8 (29.3, 41.4)	34.7 (30.3, 39.7)
Late premenopause	34.8 (30.4, 39.8)	44.4 (38.1, 51.2)	36.5 (31.5, 42.3)
Premenopause	36.4 (33.0, 40.2)	37.8 (34.4, 41.5)	34.2 (31.5, 37.2)
Testosterone (ng/dL), mean (95% confidence interval)			
Postmenopause	10.7 (7.4, 15.5)	12.5 (8.8, 17.6)	12.5 (8.9, 17.6)
Late transmenopause†	10.9 (7.8, 15.2)	13.5 (10.6, 17.2)	16.0 (13.7, 18.6)
Early transmenopause	10.8 (8.1, 14.3)	10.4 (8.6, 12.5)	10.5 (8.9, 12.4)
Late premenopause	10.2 (8.3, 12.6)	11.1 (8.7, 14.2)	12.4 (10.2, 15.1)
Premenopause	10.5 (9.1, 12.1)	10.2 (9.0, 11.6)	9.4 (8.3, 10.6)

NOTE: Geometric means and 95% confidence intervals from multiple regression models that included up to four assessments per participant and adjusted for time on study, age, smoking status, and ethnicity.
*P = 0.02, comparing highest to lowest tertiles; P = 0.07, middle to lowest tertiles; P = 0.05 in χ^2 test for linear trend.
† P = 0.01, comparing highest to lowest tertiles; P = 0.11, middle to lowest tertiles; P < 0.01, in χ^2 test for linear trend.

Table 4. Estradiol and testosterone by physical activity and body size among participants in late transition

BMI (kg/m^2)	Physical activity level		
	Most active	Middle tertile	Least active
Estradiol (pg/mL), $P_{interaction\ term} = 0.06$			
30+	32.2 (23.8, 43.4)	28.4 (20.6, 39.3)	34.4 (26.6, 44.4)
25-29.9	19.2 (8.1, 45.1)	21.2 (12.4, 36.3)	96.7 (42.3, 221.3)
<25	24.4 (15.7, 37.8)	30.4 (21.8, 42.5)	29.5 (16.9, 51.8)
Testosterone (ng/dL), $P_{interaction\ term} = 0.0001$			
30+	5.9 (3.6, 9.5)	8.9 (5.7, 13.8)	23.8 (19.0, 29.8)
25-29.9	16.9 (9.9, 29.0)	12.9 (7.3, 22.9)	19.2 (9.9, 37.1)
<25	11.4 (6.6, 19.5)	12.1 (8.2, 17.7)	12.8 (10.0, 16.4)

NOTE: Data from 98 observations contributed from 92 women. Geometric means and 95% confidence intervals from bivariate regression models that included up to four assessments per participant.

of the menopausal transition, as defined by 3 to 11 months of amenorrhea. Although not statistically significant, estradiol and testosterone were observed to be 19% and 15% lower, respectively, among postmenopausal women, who were in the highest versus lowest physical activity tertile. It is possible that the reason an association was detected among late transition, but not postmenopausal, women was that the hormone levels were higher among women in the late transition phase. On the other hand, it could be that physical activity has the potential to reduce endogenous estrogens and androgens in a specific window of time, late in the menopausal transition time period. It is also possible that the associations detected among the late transition period were due to chance.

Physical activity has been shown to be inversely associated with estrogen levels among postmenopausal women in some (13, 28-30), but not all, observational studies (31-33). Six cross-sectional studies have examined the association of exercise and hormone levels within postmenopausal women (28-33). Of these, three observed lower estradiol (28) or estrone (29, 30) levels among women who self-reported higher levels of physical activity. None of the three studies that specifically examined associations of physical activity with testosterone observed significant associations among postmenopausal women (30, 33, 34). In addition, there has been one randomized controlled trial (13) that has examined the effect of exercise on estrogens and androgens in postmenopausal women. The study included 173 postmenopausal women who were randomized to a treatment (87 women) or control (86 women) group. The physical activity intervention consisted of at least 45 min of moderate intensity sports/recreational activity 5 d/wk for 12 months. Significant reductions in serum estradiol, estrone, and testosterone were noted at 3 months. At 12 months, these results were no longer significant, except among women who had lost >2% body fat. Overall, observational studies and one experimental study have observed quite mixed results with regard to the association of physical activity in determining sex hormones after menopause.

Similar to the findings among postmenopausal women, six small experimental studies (n of 18 or less) of changes in endogenous reproductive hormones after exercise training in premenopausal women (35) also show little consistency regarding effects. A recent cross-sectional study with 139 women ages 24 to 37 years observed a strong association between estradiol and self-reported physical activity (36). The increased variability in hormone levels across the menopausal transition attenuates any differences observed. The present findings extend results of prior studies by examining the perimenopausal period, with outstanding hormonal measurement methodology (hormone levels were assessed across two menstrual cycles at each assessment period, days 1-6 of the menstrual cycle, and cycle-to-cycle variability in the day of data collection was kept to 3-4 days at each assessment period) and in a larger data set. However, these results would be made more useful if the same magnitude of effect of physical activity on estradiol and testosterone is subsequently observed in a randomized controlled trial of perimenopausal women.

We hypothesized that any observed association between physical activity and endogenous reproductive hormones among perimenopausal women would be affected by body size. The present data partly support this hypothesis, given our observation that differences in testosterone by physical activity tertile was most evident among women in the highest BMI category ($\geq$30 kg/m^2). Our results and the findings from McTiernan et al. (13, 14) and Cauley et al. (30) all concur that body size is an important variable to consider in the association of physical activity with endogenous estrogens and androgens. The relative importance of ovarian versus adipose tissue production of reproductive hormones shifts during the menopausal transition. Physical activity is thought to primarily influence hormonal activity through alterations in energy balance and body fat levels. Our findings show a significant association between physical activity and hormone levels after 3 to 11 months of amenorrhea. Therefore, it is possible that the shift from ovarian to adipose production of hormones may occur before 12 months of amenorrhea, the currently accepted definition of postmenopause.

The use of the Penn Ovarian Aging Study data for this analysis extends what has been previously reported, given the large sample size (394) and multiple assessments of physical activity and hormones as participants move through the menopausal transition. The analysis takes advantage of multiple observations over time, examines physical activity and reproductive hormone data measured concurrently from the same assessment periods, and provides information on between person physical activity and hormone associations. However, this analytic approach cannot determine the effects of within woman changes in physical activity on her hormone levels over time or determine the temporality of the reported associations. Further analysis to examine within-woman changes over time was considered, but rejected because physical activity was assessed 2 years apart, making any estimate of change over time difficult to interpret. Furthermore, few women changed their physical activity enough to discern effects of individual changes.

In summary, physical activity was observed to be inversely associated with both estradiol and testosterone levels among women in the late transition time frame of the menopausal transition. This association seems to be

moderated by body size, in that the association is clearest among those who are overweight or obese. The implications of these findings for ovarian, endometrial, and breast cancer risk will become clearer after a randomized controlled exercise intervention trial among perimenopausal women.

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