Research Article

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Effects of Exercise and Cardiorespiratory Fitness on Estrogen Metabolism in Postmenopausal Women

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Abstract

Background: Lowering endogenous estrogen levels is one mechanism whereby physical activity may lower postmenopausal breast cancer risk. Several prospective studies have suggested that increased 2-hydroxylation of estrogens may also reduce postmenopausal breast cancer risk, but whether or not exercise alters estrogen metabolism through this mechanism is unclear.

Methods: We measured total circulating concentrations of parent estrogens (estrone and estradiol) and 13 estrogen metabolites, including glucuronidated, sulfated, and unconjugated forms, by stable isotope dilution LC/MS-MS in 153 postmenopausal women randomized to 12 months of moderate-to-vigorous exercise and 153 controls. We also explored associations with cardiorespiratory fitness measured by treadmill.

Results: Although women randomized to exercise averaged 178 minutes/week of exercise over 12 months, their cardiorespiratory fitness was 13% greater than controls at 12 months ($P = 0.0001$), and total estradiol was reduced by 10% ($P = 0.04$); there were no statistically significant effects of exercise on circulating concentrations of estrogen metabolites in the 2-, 4-, or 16-pathways, or on the 2-pathway/parent estrogens ratio. However, we observed a statistically significant association between increased fitness and reduced concentration of 2-pathway metabolites ($P < 0.05$).

Conclusions: We found no evidence that 12 months of moderate-to-vigorous exercise or increased fitness changed estrogen metabolism in a way that might reduce breast cancer risk.

Impact: The protective effect of exercise on postmenopausal breast cancer is unlikely to be mediated by changes in estrogen metabolism. *Cancer Epidemiol Biomarkers Prev; 27(12); 1480–2. ©2018 AACR.*

Introduction

Reduction of endogenous estrogen levels is one mechanism whereby physical activity may lower breast cancer risk (1, 2), but whether exercise also alters the metabolism of estrogen in a way that influences risk is uncertain. Estrone and estradiol, the parent estrogens, are metabolized via irreversible hydroxylation at the 2-, 4-, or 16-position of the steroid ring (3). Preferential metabolism of estrogens through the 2-pathway is associated with lower postmenopausal breast cancer risk (4), even after adjusting for the influence of estradiol (5). In a randomized trial in postmenopausal women, exercise had no effect on the urinary 2-hydroxyestrone/16α-hydroxyestrone ratio (6), an early measure of preferential metabolism via the 2-pathway. However, in a cross-sectional study in premenopausal women using a comprehensive measure of 13 urinary estrogen metabolites, exercise appeared to enhance 2-hydroxylation (7), perhaps by modulating the activity of p450 enzymes. To clarify these discrepant findings, we tested the hypothesis that 12 months of exercise in postmenopausal women would enhance metabolism of estrogens through the 2-pathway by using LC/MS-MS to measure total serum concentrations of estrone, estradiol, and 13 downstream metabolites. We also explored relations between estrogen metabolism and cardiorespiratory fitness.

Materials and Methods

The Alberta Physical Activity and Breast Cancer Prevention (ALPHA) Trial investigates biological mechanisms linking exercise to postmenopausal breast cancer (1). Eligible women were 50 to 74 years, reported being postmenopausal for at least 24 months, had a body mass index (BMI) of 22 to 40 kg/m^2, and were inactive (exercise < 90–120 minutes/week) and/or unfit (VO_2 < 34.5 mL/kg/min). They had no major comorbidities and were not using menopausal hormone therapy. The study was powered to detect a 14% reduction in circulating estradiol (1).

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Table 1. ALPHA baseline values and main effects for estrogens, estrogen metabolites, and metabolic pathways

Estrogens, estrogen metabolites, and metabolic pathways[a]	Serum concentrations at baseline (pmol/L) Exercisers ($n = 153$) Mean (SE)	Controls ($n = 153$) Mean (SE)	Main effects between groups % Difference[b] (SE)
Parent estrogens	379.6 (13.8)	389.3 (29.1)	−5.3 (3.8)
Estrone	339.5 (12.3)	341.2 (12.8)	−4.5 (3.9)
Estradiol	40.1 (2.5)	48.1 (4.9)	**−10.0 (4.7)**[c]
2-pathway	183.5 (4.7)	191.4 (6.4)	−2.1 (2.9)
2-Hydroxyestrone	82.2 (2.6)	87.7 (3.6)	−1.9 (3.8)
2-Hydroxyestradiol	27.5 (1.0)	28.6 (1.2)	−5.7 (4.7)
2-Methoxyestrone	42.6 (1.4)	43.2 (1.6)	−4.1 (3.3)
2-Methoxyestradiol	22.9 (0.7)	23.6 (0.7)	0.6 (3.4)
2-Hydroxyestrone-3 methyl ether	8.2 (0.2)	8.3 (0.3)	1.2 (3.6)
4-pathway	21.1 (0.5)	21.6 (0.6)	2.7 (2.5)
4-Hydroxyestrone	9.9 (0.3)	10.2 (0.4)	4.1 (3.7)
4-Methoxyestrone	6.1 (0.2)	6.0 (0.2)	−1.2 (3.0)
4-Methoxyestradiol	5.2 (0.2)	5.4 (0.2)	4.8 (3.4)
16-pathway	254.9 (8.1)	252.6 (8.7)	1.3 (3.6)
16α-hydroxyestrone	37.5 (1.2)	39.2 (1.5)	−2.5 (3.8)
17-Epiestriol	12.5 (0.4)	12.8 (0.5)	3.2 (4.0)
Estriol	144.9 (5.2)	141.5 (5.4)	1.8 (4.2)
16-Ketoestradiol	42.5 (1.5)	42.0 (1.5)	3.5 (3.8)
16-Epiestriol	17.5 (0.5)	17.2 (0.5)	2.4 (3.6)
2-pathway/parent estrogens ratio	0.53 (0.01)	0.54 (0.01)	3.0 (3.1)

[a]Includes glucuronidated, sulfated, and unconjugated forms for each estrogen, estrogen metabolite, and metabolic pathway.
[b]% Difference derived from linear mixed models adjusted for baseline estrogen/estrogen metabolite concentrations, without adjustment for weight change: 153 exercisers and 154 controls. Significant differences are in bold.
[c]$P = 0.04$.

Women were randomized to exercise or a wait-list control group for 12 months. The exercise goal was 5 days/week, 45 minutes/day at 70% to 80% of heart rate reserve.

Cardiorespiratory fitness was estimated with a treadmill protocol and weight was measured at baseline, 6, and 12 months. Fasting (10+ hours) blood samples were collected at baseline and 12 months. Of 320 participants, 307 still had blood samples from both time points: 153 exercisers and 154 controls (See Supplementary Fig. S1). Total concentrations (including glucuronidated, sulfated, and unconjugated forms) of estrone, estradiol, and 13 estrogen metabolites were assayed using stable isotope dilution LC/MS-MS (3). Assay batches had equal number of exercisers and controls, and both samples from individual participants were placed in the same batch. Laboratory CVs from blinded quality control samples were low (0.7%–3.9%).

Wilcoxon rank-sum and χ^2 tests were used to evaluate group differences at baseline. The effect of exercise on estrogen metabolism measures was examined with intention-to-treat analysis using linear mixed models, adjusting for baseline values, with and without adjustment for weight change. Linear regression was used to evaluate cross-sectional and longitudinal associations between estrogen metabolism and fitness.

Results

Participants were, on average, 61 years of age, with a BMI of 29 kg/m^2, and predominantly Caucasian (91%). There were no differences in participant characteristics or estrogen, estrogen metabolite, or metabolic pathway concentrations between exercise and control groups at baseline (Table 1). Exercisers completed an average of 178 minutes/week of exercise over 12 months, had 13% higher cardiorespiratory fitness than controls ($P = 0.0001$) at the end of the trial, and lost 2.3 kg of weight (4).

Table 2. Correlations between cardiorespiratory fitness and estrogen metabolism measures: cross-sectional at baseline and longitudinal changes over time

Estrogens, estrogen metabolites, and metabolic pathways[a]	Cross-sectional at baseline[b] *R*	Changes over time[c] *R*
Parent estrogens	−0.03	−0.05
Estrone	−0.02	−0.05
Estradiol	−0.08	−0.07
2-pathway	**−0.15**	**−0.14**
2-Hydroxyestrone	**−0.18**	**−0.14**
2-Hydroxyestradiol	−0.08	−0.10
2-Methoxyestrone	−0.04	−0.03
2-Methoxyestradiol	−0.06	−0.08
2-Hydroxyestrone-3 methyl ether	−0.03	−0.11
4-pathway	−0.08	−0.09
4-Hydroxyestrone	**−0.13**	−0.08
4-Methoxyestrone	−0.01	−0.08
4-Methoxyestradiol	0.03	−0.02
16-pathway	−0.03	−0.07
16α-hydroxyestrone	−0.07	−0.02
17-Epiestriol	−0.02	−0.07
Estriol	−0.01	−0.08
16-Ketoestradiol	−0.04	−0.04
16-Epiestriol	−0.07	−0.09
2-pathway/parent estrogens ratio	−0.10	−0.10

[a]Includes glucuronidated, sulfated, and unconjugated forms for each estrogen, estrogen metabolite, and metabolic pathway.
[b]On the basis of linear regression of fitness on estrogen metabolism measures, adjusted for age, education, ethnicity, family history of breast cancer, energy intake, and BMI at baseline. Includes both exercise and control arms. Significant correlations are in bold.
[c]On the basis of linear regression of fitness change scores between baseline and 12 months on changes in estrogen metabolism measures over the same time interval, adjusted for age, education, ethnicity, family history of breast cancer, energy intake, and weight change over time. Includes both exercise and control arms. Significant correlations ($P < 0.05$) are in bold.

Although exercise decreased total estradiol by 10% ($P = 0.04$), there were no significant effects on concentrations of estrogen metabolites in the 2-, 4-, or 16-pathway, or on the 2-pathway/parent estrogens ratio—our indicator of preferential metabolism through the 2-pathway (Table 1). Results remained null after adjusting for weight change or stratifying by exercise adherence.

In cross-sectional analyses, higher cardiorespiratory fitness was significantly associated with lower 2-pathway and 2- and 4-hydroxyestrone concentrations ($r = -0.13$ to -0.18), after adjustment for BMI (Table 2). In longitudinal analyses, increased fitness was significantly associated with lower 2-pathway and 2-hydroxyestrone concentrations ($r = -0.14$), after adjustment for weight change.

Discussion

Using a comprehensive LC/MS-MS measure of circulating concentrations of 13 estrogen metabolites that has provided new insights into the role of estrogen metabolism in breast carcinogenesis (4, 5), we found that 12 months of moderate-to-vigorous exercise by postmenopausal women had no obvious effect on estrogen metabolism or, more specifically, on preferential metabolism of estrogens through the 2-pathway. This finding is consistent with a previous trial in postmenopausal women that found no changes in urinary 2-hydroxyestrone, 16α-hydroxyestrone, or their ratio (6), but differs from two studies of urinary estrogen metabolism in premenopausal women, which suggest that exercise may enhance estrogen metabolism through the 2-pathway (7, 8). In contrast, increased cardiorespiratory fitness was associated with significantly lower levels of 2-pathway estrogen metabolites, a metabolic response inconsistent with lower breast cancer risk (4). Overall, these findings suggest that the protective effect of exercise on postmenopausal breast cancer is mediated, in part, by reductions in estradiol rather than a beneficial effect on the downstream metabolism of estrogen.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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