

Null Results in Brief

No Effect of Exercise on Insulin-Like Growth Factor 1 and Insulin-Like Growth Factor Binding Protein 3 in Postmenopausal Women: a 12-Month Randomized Clinical Trial

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Introduction

A meta-analysis indicated that increased circulating concentrations of insulin-like growth factor 1 (IGF-1) are associated with increased risks for colorectal, prostate, and premenopausal breast cancers, and that increased concentrations of IGF binding protein 3 (IGFBP-3) are associated with increased risk of premenopausal breast cancer (1). Little is known about whether serum concentrations of IGF-1 or IGFBP-3 can be modified, although authors have suggested that diet, exercise, or adiposity may affect concentrations of these proteins (2, 3). Women who engage in regular physical activity have a reduced risk for both colon and breast cancers compared with inactive women (4). A testable and reasonable hypothesis is that reduction of circulating IGF-1 concentrations or increase in IGFBP-3, resulting in less free IGF-1, or a reduction in the ratio of IGF-1 to IGFBP-3 would lower breast and colon cancer risk. We conducted a randomized clinical trial to examine the effect of a 12-month moderate-intensity exercise intervention on serum IGF-1, IGFBP-3, and their ratio in sedentary, overweight/obese postmenopausal women not taking hormone therapy.

Methods

The study was a randomized clinical trial comparing the effect of a 12-month moderate-intensity aerobic exercise intervention versus stretching control program on hormones and body composition measured at baseline, 3 months, and 12 months (5). All study procedures, including written informed consent, were reviewed and approved by the Fred Hutchinson Cancer

Research Center Institutional Review Board. Participants were women, ages 50 to 75 years, sedentary, with a body mass index ≥ 25.0 kg/m² (or a body mass index between 24.0 and 25.0 kg/m² if percent body fat measured by bioelectrical impedance was greater than 33.0%), not taking hormone therapy in any form in the past 6 months, and healthy. We randomly assigned women to an exercise intervention ($n = 87$) or a control group ($n = 86$).

The exercise prescription consisted of at least 45 minutes of moderate-intensity exercise 5 days a week for 12 months (5). Control participants attended a 45-minute stretching session once a week for 12 months.

At baseline, 3 months, and 12 months, we collected demographic information, medical history, health habits, medication use, reproductive and body weight history, total energy intake over the previous 3 months via a 120-item self-administered food frequency questionnaire (6), anthropometrics, and body composition (via DEXA, Hologic QDR 1500, Hologic, Inc., Waltham, MA). Participants provided a 12-hour-fasting 50-mL sample of blood at the three time points.

IGF-1 and IGFBP-3 assays were done on serum at the Reproductive Endocrine Research Laboratory (University of Southern California, F. Stanczyk, Director). IGF-1 was quantified via a two-site chemiluminescence immunoassay using the Nichols Advantage Specialty System (Nichols Diagnostic Institute, San Juan Capistrano, CA). The intra- and interassay CVs were 2.5% and 7.0%, respectively. IGFBP-3 was quantified via a sensitive and specific competitive protein-binding RIA using the IGFBP-3 100T Kit from Nichols Diagnostics Institute. The intra- and interassay CVs were 7.8% and 13.2%, respectively. All samples from a participant were assayed together.

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). The analysis considered log-transformed hormone measures 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. We had greater than 80% power to detect a difference in change from baseline to 12 months between exercisers and controls of 8.19 ng/mL for IGF-1 and 0.36 μ g/mL for IGFBP-3. For secondary analyses, we examined whether the effect of exercise on hormone concentrations and their ratio varied with the degree of change in percent body fat or, among

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Note: B. Sorensen and Y. Yasui did the data analyses.

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Table 1. Geometric means (95% confidence intervals) for IGF-1 and IGFBP-3 for postmenopausal women randomized to aerobic exercise intervention vs. control group (stretching) at baseline, 3 mo, and 12 mo

	Baseline		3 mo		<i>P</i> *	12 mo		<i>P</i> [†]
	Exercisers	Stretchers	Exercisers	Stretchers		Exercisers	Stretchers	
IGF-1, ng/mL	99 (91-107)	103 (97-110)	94 (87-102)	100 (92-108)	0.65	97 (89-106)	102 (94-110)	0.99
IGFBP-3, µg/mL	3.95 (3.72-4.20)	3.84 (3.59-4.11)	3.58 (3.35-3.83)	3.70 (3.45-3.96)	0.13	3.71 (3.45-4.00)	3.63 (3.37-3.91)	0.88
IGF-1/IGFBP-3	25.0 (23.2-27.0)	26.9 (25.2-28.7)	26.2 (24.4-28.3)	27.0 (25.0-29.0)	0.29	26.1 (23.9-28.6)	28.0 (25.7-30.5)	0.90

*Difference in protein change from baseline to 3 months in exercisers versus controls.

† Difference in protein change from baseline to 12 months in exercisers versus controls.

exercisers only, with minutes exercised per week or change in VO_{2max} . All statistical tests were two sided. Statistical analyses were done using SAS software (version 8.2, SAS Institute, Inc., Cary, NC).

Results

Blood samples were available for all 173 women at 3 months and for 170 women at 12 months. At baseline, the intervention and control groups were similar with regard to demographic characteristics, body composition, mean daily caloric intake, fitness levels, and hormone concentrations (all $P > 0.05$). Participants on average were 61 years old and obese (mean body mass index, 30.4), and 86% were non-Hispanic White, 4% were African-American, and 6% were Asian-American.

On average over the 12 months, the exercisers participated in moderate-intensity sports/recreational activity for a mean (SD) of 3.7 (1.4) days per week for a total of 171 (87.9) minutes per week (versus goal 225 minutes/wk). Six (8%) exercisers "dropped out" of the intervention (all after 3 months). On average, VO_{2max} increased in exercisers by 12.7% and in controls by 0.8% ($P < 0.0001$).

IGF-1 concentrations decreased slightly, but not statistically significantly, in both exercisers and controls in the first 3 months, then reverted to close to baseline values by 12 months (Table 1). IGFBP-3 decreased slightly in exercisers and controls, and the difference comparing exercisers and controls was not statistically significant. The change in the ratio of IGF-1 to IGFBP-3 did not differ between exercisers and controls. Adjustment for changes in caloric, dairy, and alcohol intake did not change the results. No consistent effects by age, body mass index, or change in VO_{2max} were observed on the change in IGF-1, IGFBP-3, or their ratio over 3 or 12 months (data not shown).

Discussion

The results of this randomized clinical trial suggest that a moderate-intensity exercise intervention has minimal to no

effect on concentrations of IGF-1, IGFBP-3, or their ratio. The study had excellent retention and adherence, which decreases the chance of biased results and increases study power. A small number of randomized clinical trials have reported on the effect of aerobic or strength-training exercise on IGF or its binding proteins, with mixed results (7). Given the disparate results in this handful of small studies, the effects of exercise on IGF and its binding proteins in healthy postmenopausal women are still unknown.

Our study suggests that moderate-intensity aerobic exercise does not affect concentrations of IGF-1, IGFBP-3, or their ratio in overweight/obese previously sedentary postmenopausal women. If other studies confirm this, then other interventions will need to be identified that can change the levels of these intriguing cancer biomarkers.

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