

Randomized Controlled Trial of Aerobic Exercise on Insulin and Insulin-like Growth Factors in Breast Cancer Survivors: The Yale Exercise and Survivorship Study

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Abstract

Background: High insulin and insulin-like growth factor-I (IGF-I) levels may be associated with an increased breast cancer risk and/or death. Given the need to identify modifiable factors that decrease insulin, IGF-I, and breast cancer risk and death, we investigated the effects of a 6-month randomized controlled aerobic exercise intervention versus usual care on fasting insulin, IGF-I, and its binding protein (IGFBP-3) in postmenopausal breast cancer survivors.

Methods: Seventy-five postmenopausal breast cancer survivors were identified from the Yale-New Haven Hospital Tumor Registry and randomly assigned to an exercise ($n = 37$) or usual care ($n = 38$) group. The exercise group participated in 150 minutes per week of moderate-intensity aerobic exercise. The usual care group was instructed to maintain their current physical activity level. A fasting blood sample was collected on

each study participant at baseline and 6 months. Blood levels of insulin and IGF were measured with ELISA. **Results:** On average, exercisers increased aerobic exercise by 129 minutes per week compared with 45 minutes per week among usual care participants ($P < 0.001$). Women randomized to exercise experienced decreases in insulin, IGF-I, and IGFBP-3, whereas women randomized to usual care had increases in these hormones. Between-group differences in insulin, IGF-I, and IGFBP-3 were 20.7% ($P = 0.089$), 8.9% ($P = 0.026$), and 7.9% ($P = 0.006$), respectively.

Conclusions: Moderate-intensity aerobic exercise, such as brisk walking, decreases IGF-I and IGFBP-3. The exercise-induced decreases in IGF may mediate the observed association between higher levels of physical activity and improved survival in women diagnosed with breast cancer. (Cancer Epidemiol Biomarkers Prev 2009;18(1):306–13)

Introduction

There has been increasing evidence that high insulin levels increase the risk of breast cancer recurrence and death (1-3). Three recent studies have observed an approximate triple risk of all-cause mortality among women in the highest category of insulin or c-peptide, a marker of insulin secretion, relative to the lowest category of insulin or c-peptide (1-3). These studies have also shown that high insulin and c-peptide levels are strongly associated with obesity and low levels of physical activity (1, 4), both adverse prognostic factors in women diagnosed with breast cancer (5-9). Specifically, several recent observational studies have suggested that women who participate in 2 to 3 hours per week of moderate-intensity aerobic exercise, such as brisk walking, after a diagnosis of breast cancer have a 40% to 67% reduced risk of death (7-9). Although the mechanisms linking exercise to breast cancer prognosis are not well understood, insulin may prove to be the elusive link

between low levels of physical activity and poor breast cancer prognosis. Thus, therapies to reduce insulin levels in breast cancer survivors could dramatically decrease breast cancer-related deaths. A lowering of insulin levels by 25% may improve survival by 5%, the same order of magnitude as the beneficial effect of adjuvant chemotherapy (1, 10). Given that many existing breast cancer therapies are costly and have significant side effects that can result in long-term morbidity, non-pharmacologic methods to lower insulin levels and ultimately breast cancer recurrence and death, especially methods that are also associated with improvements in quality of life and other chronic diseases, may offer an attractive addition to the currently available treatment options.

Despite a growing body of research, evidence supporting the association between exercise and insulin in breast cancer survivors has remained somewhat inconclusive (11-13); yet, the possibility that exercise may act as a targeted therapy in breast cancer is intriguing and warrants further investigation. Therefore, the purpose of the Yale Exercise and Survivorship (YES) study was to examine the effects of a 6-month randomized controlled aerobic exercise intervention versus usual care on fasting insulin levels in postmenopausal breast cancer survivors who completed adjuvant therapy.

Secondary aims were to examine the effect of exercise on insulin-like growth factor-I (IGF-I) and its primary

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binding protein (IGFBP-3). Similar to insulin, IGF-I has potent mitogenic and antiapoptotic properties in normal and malignant breast epithelial cells, whereas IGFBP-3 can either stimulate or suppress cellular proliferation by restricting the availability and biological activity of IGF-I (14). For insulin, some mitogenic effects may be mediated by interaction with IGF-I receptors, as hyperinsulinemia promotes the synthesis and activity of IGF-I (15). Although the data are not consistent, high levels of IGF-I and low levels of IGFBP-3 have been associated with an increased risk of breast cancer and adverse prognostic factors (16, 17); however, a study by Goodwin and colleagues that found high levels, rather than low levels, of IGFBP-3 predicted distant recurrence of breast cancer in postmenopausal women (18). In healthy women, the effect of exercise on IGF has been somewhat inconsistent (19, 20), and to date, only two trials have examined the effect of exercise on IGF in breast cancer survivors (12, 13), with only one study observing a significant effect of exercise on IGF (12).

Last, our tertiary aim was to examine what factors may modify the effect of exercise on insulin and IGF, including stage at diagnosis, hormone therapy, age, body mass index (BMI), and change in body weight or fat. To our knowledge, no other study has examined whether certain prognostic or physiologic factors modify the effect of exercise on insulin and IGF. We hypothesized that exercise would be associated with favorable changes in insulin and IGF, and that stage at diagnosis, hormone therapy, age, BMI, and weight or fat loss would modify the effect of exercise on insulin and IGF.

Materials and Methods

Participants were recruited into the YES study, which is described in detail elsewhere (21, 22). All study procedures were reviewed and approved by the Yale University School of Medicine Human Investigation Committee.

Study Participants. Participants were physically inactive (<60 min/wk of recreational physical activity reported in the past 6 mo), postmenopausal women (i.e., cessation of menses for at least 12 mo) diagnosed 1 to 10 y ago with stage 0 to IIIA breast cancer and who had completed adjuvant treatment at least 6 mo before enrollment. Smokers, women with type 2 diabetes, and women with a previous cancer, recurrence, or second cancer were excluded due to the potential effect of these factors on outcomes of interest.

Recruitment. Study staff used the Yale-New Haven Tumor Registry to obtain the names of Connecticut women diagnosed with breast cancer by any Yale-affiliated physician from March 1994 to January 2006 (Fig. 1). Staff contacted each patient's physician to request permission to contact the participant. An invitation letter was mailed to the participant, followed by a telephone screening questionnaire, baseline and 6-mo clinic visit. From 788 screening calls made, 75 (9.5%) women were eligible, interested, and randomized.

Measures

Physical Activity. At baseline and 6 mo, participants completed an interviewer-administered physical activity

questionnaire, assessing the past 6 mo of recreational activity (23), a 7-d physical activity log (24), and a 7-d pedometer log (25). For the physical activity log, women recorded the type and duration of any recreational activity done on each day. Hours per week spent in moderate- to vigorous-intensity aerobic activity were determined using Ainsworth's Compendium of Physical Activities (26).

Demographics and Medical History. Information was collected via an interviewer-administered questionnaire at the baseline visit. Information about disease stage, hormone receptor status, adjuvant therapy, and surgery was provided by participants and later confirmed by their physician and review of the medical records.

Anthropometry. Height and weight were measured at baseline and 6 mo. Participants were weighed on a digital scale in light clothing, without shoes; measurements were rounded up to the next 0.1 kg. Height without shoes was measured using a stadiometer, rounding up to the next 0.5 cm. Circumference measurements were taken at the waist (minimum circumference) and hips (greatest circumference). All measurements were taken twice in succession, by the same technician, and averaged for data entry.

Dual-Energy X-ray Absorptiometry Scans. A dual-energy X-ray absorptiometry (DEXA) scan was completed for each participant at baseline and 6 mo (27). The DEXA measurements were made with a Hologic scanner (Hologic 4500, Hologic Inc.) that was calibrated daily. The coefficient of variation for repeat assessment of body fat, lean mass, and bone mineral density (BMD) is <1%. All DEXA scans were evaluated by one radiologist blinded to the intervention group of the participant.

Food Frequency Questionnaire. All participants completed a 120-item validated food frequency questionnaire at baseline and 6 mo (28). Although participants were advised to maintain their current dietary habits, we measured their dietary habits to control for any changes in diet over the 6-mo time period.

Blood Draws and Serologic Assays. A fasting blood draw (≥ 12 h) was done on each study participant at baseline and 6 mo. To reduce random or systematic variation in assay results, baseline and 6-mo specimens collected from the same women were assayed simultaneously at the end of the study, and both intervention and control participants were included in each batch of assays. Samples were measured in duplicate to improve reliability. Quality control samples, measuring low and high ranges for each hormone, were included with each batch. Laboratory technicians were blinded to treatment assignment.

Insulin was measured in serum using an ELISA kit (DSL-10-1600, Diagnostic Systems Laboratories, Inc.). The laboratory test was done following the assay manual. The mean intra-assay coefficient of variation for the low- and high-range quality control samples were 7.4% and 5.4%, respectively.

Commercial ELISA kits from Diagnostic Systems Laboratories, Inc., were also used to measure plasma concentrations of total IGF-I and IGFBP-3 following the manufacturer's instructions. For IGF-I, the mean intra-assay coefficient of variation was 2.8% for low values and

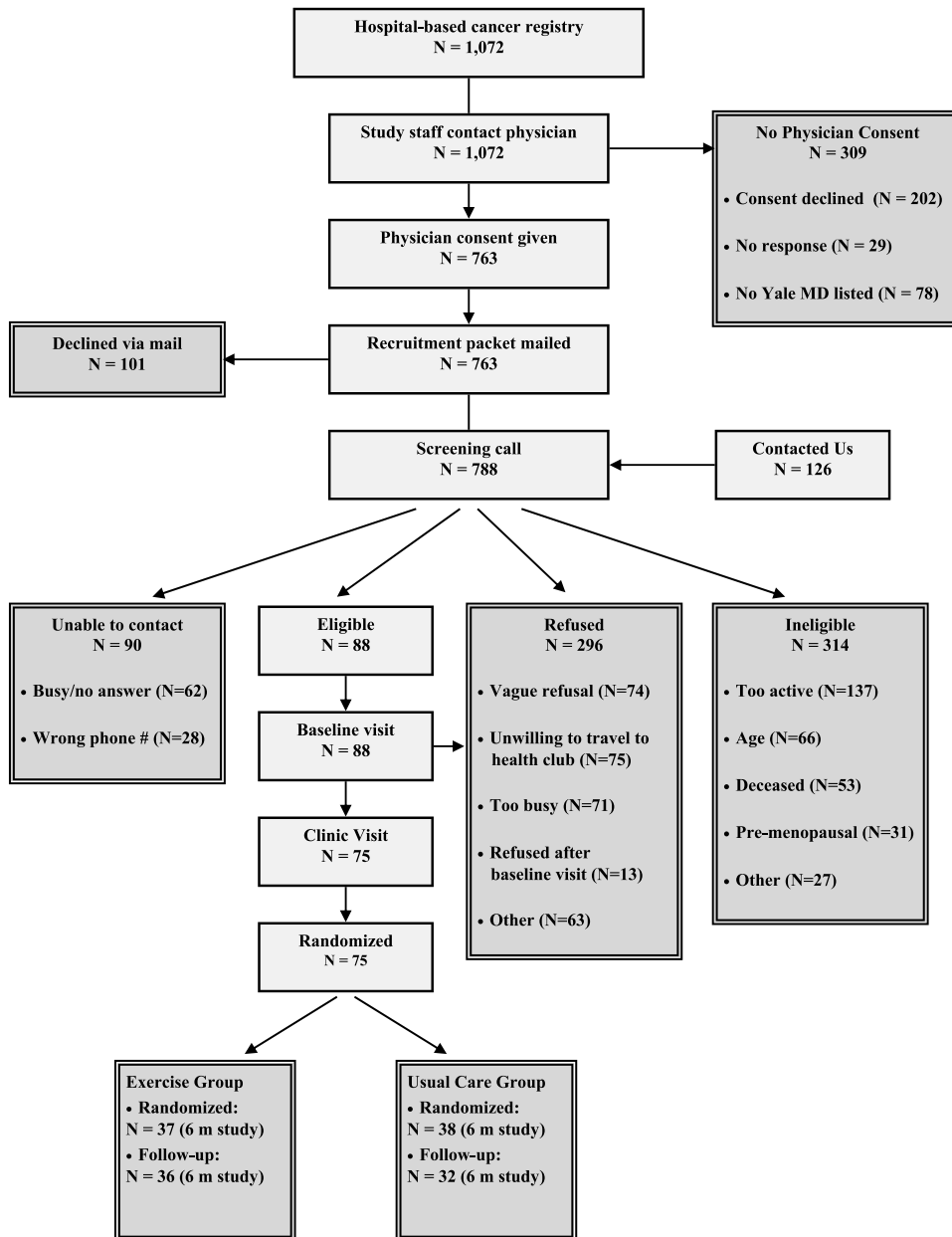


Figure 1. Flow of participants through the YES study.

0.7% for high values. For IGFBP-3, the mean coefficients of variation for low- and high-range quality control samples were 6.6% and 3.2%, respectively.

Exercise Intervention. The exercise intervention consisted of a combined supervised training program at a local health club and a home aerobic training program. Participants exercised at the health club during designated sessions three times per week and were instructed to exercise 2 d/wk on their own, either at the health club or at home. Participants were asked to do three 15-min sessions during week 1, building to five 30-min moderate-intensity sessions by week 5, the current physical activity recommendation for adults (29). Participants wore heart rate monitors during each workout. Following each exercise session, participants recorded the type,

duration, perceived intensity of activity, and average heart rate during exercise in physical activity logs. Participants returned logs to the exercise physiologists at the end of each week.

The intervention consisted primarily of walking, an activity preferred by breast cancer survivors (30), although participants could choose to meet the exercise goal through other forms of aerobic activity. Activities that did not involve sustained aerobic effort, such as resistance training and yoga, could be done but did not count toward the exercise goal for each week.

Usual Care Group. Women in the usual care group were instructed to continue with their usual activities. If a participant wanted to exercise, she was told she could but that our exercise program and training materials

would not be offered to her until the end of the study. At the end of the study, women were offered three supervised training exercise sessions, a pedometer, exercise handouts, and results of clinical tests. All study participants also received quarterly newsletters that focused on issues related to breast cancer survivorship.

Randomization. After completion of all baseline measures, each participant was randomly assigned to either the exercise or usual care group using a random number generation.

Statistical Analyses. Data were analyzed using SAS version 9.1. Participants were grouped according to the intention-to-treat procedure in which all participants were grouped according to their intervention assignment at randomization; however, women with missing hormone values were excluded from analysis ($n = 7$). One woman's 6-mo insulin value was 224% greater than her baseline value (baseline insulin = 37.8 $\mu\text{U}/\text{mL}$, 6-mo insulin = 122.5 $\mu\text{U}/\text{mL}$) and most likely associated with her recent chemotherapy-induced menopause. Therefore, this woman was excluded from the insulin analyses. We used t tests and χ^2 analyses to assess between-group baseline differences. Intervention effects were evaluated by the differences in the mean changes at 6 mo between the intervention and usual care groups using the generalized estimating equation modification to linear regression models to account for the longitudinal nature of the data. As the two study groups did not differ at baseline, analyses only adjusted for baseline insulin, IGF-I, or IGFBP-3 were done. We also explored a priori effect modification by disease stage, hormone therapy, age, BMI, and change in body weight or fat. Last, for exercisers only, we examined changes in insulin and IGF based on adherence levels and change in pedometer steps to determine if a dose-response relationship exists.

Results

Baseline Characteristics. Baseline demographic and physiologic data in the exercise and usual care groups were similar (Table 1). The average age of study participants was 56 years. The majority (84%) of participants were non-Hispanic white. The average time since diagnosis for participants was 3.3 years. Women were, on average, obese and physically inactive. Baseline levels of insulin, IGF-I, and IGFBP-3 did not differ between the groups.

Change in Physical Activity Levels and Adherence to the Exercise Intervention. Based on information reported in the 7-day physical activity log at baseline and 6 months, exercisers, on average, increased moderate- to vigorous-intensity recreational activity by 129 minutes per week at 6 months ($P < 0.001$) compared with smaller increases among usual care participants (45 minutes per week at 6 months; data not shown). Exercisers also increased their pedometer steps per day, on average, by 1,621 steps (0.9 of a mile per day) compared with 85 steps per day (0.05 of a mile per day) among usual care participants (data not shown).

Exercise group participants also completed physical activity logs each week of the intervention. They did an average of 120 minutes per week of moderate- to vigorous-intensity recreational activity for over

6 months. A total of 73% were completing at least 80% of the exercise goal of 150 minutes per week for over 6 months (data not shown). Last, women randomized to exercise chose weight-bearing aerobic activities most often, with 82% walking. Few women reported doing resistance training (3%).

Effect of Exercise versus Usual Care on Changes in Insulin and IGF. We observed a 1.75 $\mu\text{U}/\text{mL}$ (7.1%) reduction in insulin levels among exercisers and a 3.49 $\mu\text{U}/\text{mL}$ (13.6%) increase among controls, resulting in a 20.7% between-group difference during the course of the study, achieving borderline statistical significance ($P = 0.089$; Table 2). Significant differences between groups were observed for changes in both IGF-I and IGFBP-3. A 9% between-group difference in IGF-I ($P = 0.026$) was observed in exercisers compared with controls. IGF-I decreased by 7.36 ng/mL (3.4%) in the exercise group whereas controls experienced a 12.70 (5.5%) increase. Similarly, levels of IGFBP-3 decreased by 0.19 $\mu\text{g}/\text{mL}$ (4.6%) in the intervention group versus a 0.15 $\mu\text{g}/\text{mL}$ (3.3%) increase in the control group, resulting in an overall 7.9% between-group difference ($P = 0.006$).

Effect of Exercise on Insulin and IGF Stratified by Adherence. Table 3 presents the results of subgroup analyses examining adherence to the intervention among

Table 1. Baseline characteristics of randomized participants in the YES study (N = 68)

	Exercisers mean (SD) or %	Usual care mean (SD) or %
<i>n</i>	36	32
Age (y)	56.4 (9.5)	55.6 (7.7)
Ethnicity		
Non-Hispanic white	83%	90%
African-American	17%	7%
Asian or Pacific Islander	0%	3%
Education (%)		
High school graduate	17	19
Some school after high school	25	31
College graduate +	58	50
Time since diagnosis (y)	3.6 (2.2)	3.3 (2.6)
Disease stage (%)		
<i>In situ</i>	11	13
Stage I	56	25
Stage II	25	44
Stage IIIA	8	19
Treatment (%)		
None	6	16
Radiation only	42	22
Chemotherapy only	19	22
Radiation and chemotherapy	33	41
Hormone therapy (%)		
None	42	28
Tamoxifen	31	25
Aromatase inhibitors	28	47
Weight (kg)	81.0 (16.8)	79.3 (21.3)
BMI (kg/m^2)	30.4 (6.0)	30.1 (7.4)
Percent body fat (DEXA)	41.3 (6.4)	39.4 (5.9)
Physical activity Questionnaire (min per wk recreational exercise)	13.0 (24.0)	12.0 (20.0)
Daily activity log (min/wk recreational exercise)	30.0 (41.1)	11.3 (24.8)
Pedometer steps per day	5,083 (2,312)	5,624 (2,744)

NOTE: No statistically significant differences between exercise and usual care groups at baseline were observed.

Table 2. Concentrations of insulin, IGF-I, and IGFBP-3 at baseline and 6 months for exercisers (n = 36) versus usual care (n = 32) [mean (SE)]

	Baseline			6 mo			Change over 6 mo*		
	Exercisers	Usual care	P	Exercisers	Usual care	P	Exercisers	Usual care	P
Insulin ($\mu\text{U/mL}$)	24.57 (3.85)	25.69 (4.21)	0.84	22.92 (3.25)	31.98 (5.46)	0.16	-1.75 (2.32)	3.49 (2.46)	0.089
IGF-I (ng/mL)	213.34 (12.57)	232.34 (18.65)	0.40	207.14 (11.20)	243.73 (18.47)	0.10	-7.36 (6.02)	12.70 (6.39)	0.026
IGFBP-3 ($\mu\text{g/mL}$)	4.15 (0.16)	4.48 (0.17)	0.16	3.98 (0.16)	4.61 (0.18)	0.011	-0.19 (0.08)	0.15 (0.10)	0.006

*Adjusted for baseline value.

the exercise group only. Exercisers were stratified according to adherence (greater than versus less than 120 minutes per week of recreational or sport activity assessed by 7-day physical activity log) and change in pedometer steps (greater than versus less than 1 mile per day measured by pedometer). Although a nonsignificant dose-response effect was observed, decreases in insulin and IGF were observed for women exercising at lower and higher amounts.

Effect of Exercise on Insulin and IGF Stratified by Potential Effect Modifiers. Stratification by age, baseline BMI, change in body fat, disease stage, and hormone therapy did not modify the effect of exercise on insulin or IGF (Table 4). However, stronger effects of exercise on insulin and IGF were observed among older women compared with younger women.

Discussion

In our study, moderate-intensity aerobic exercise, such as brisk walking, was associated with statistically significant decreases in IGF-I and IGFBP-3. Exercise was also associated with a borderline statistically significant decrease in insulin levels. If we assume the between-group difference in IGF and insulin minimizes the adverse associations among IGF, insulin, and breast cancer risk or prognosis that have recently been reported (1-3), then the beneficial effect of exercise is comparable with that of many commonly used adjuvant chemotherapies (10). The approximate 9% between-group difference in IGF-I levels is clinically meaningful and roughly half the change that has been observed with a 20 mg/d dose of tamoxifen (31).

Whereas three other studies have examined the effect of exercise on insulin (two of the studies also examined

IGF) in breast cancer survivors (11-13), only the study conducted by Ligibel and colleagues showed a statistically significant decrease in insulin levels (11). Participants in their study were asked to participate in twice-weekly supervised strength training sessions and 90 minutes per week of home-based aerobic exercise for 16 weeks. The intervention resulted in a significant 28% reduction in insulin levels; however, IGF were not measured. Fairey and colleagues examined the effect of exercise on insulin and IGF in breast cancer survivors randomized to a thrice-weekly supervised program of 30-minute stationary bicycling for 15 weeks (12). Although participants in their study exercised for 98% of the prescribed exercise sessions, no significant differences between groups were observed for changes in insulin. However, significant differences between groups were observed for changes in IGF-I (-10.9%) and IGFBP-3 (-8.4%). Last, Schmitz and colleagues examined the effect of a twice-weekly resistance training program on insulin and IGF (13). Whereas participants were also highly adherent, there were no exercise effects on insulin, IGF-I, or IGFBP-3. Given that Ligibel's study and our study enrolled sedentary obese breast cancer survivors resulting in higher baseline insulin concentrations, compared with more active and leaner women enrolled in Fairey and Schmitz's studies, resulting in lower baseline insulin concentrations, exercise may only have a beneficial effect among heavier, less active women, who also have higher insulin levels. A similar type and dose of weight-bearing aerobic exercise has been shown to significantly lower insulin, but not IGF-I levels, in healthy, yet sedentary and obese, women (32). Last, our effect of exercise on insulin was stronger in older women. IGF-I and IGFBP-3 levels increase from birth until puberty, after which they continuously decline (33). Our finding of a stronger effect of exercise on insulin and

Table 3. Change over 6 months in insulin, IGF-I, and IGFBP-3 stratified by adherence and change in pedometer steps, exercisers only [mean (SE)]

	$\Delta\text{Insulin}$ ($\mu\text{U/mL}$)	P	$\Delta\text{IGF-I}$ (ng/mL)	P	$\Delta\text{IGFBP-3}$ ($\mu\text{g/mL}$)	P
Daily activity log over 6 mo*						
<120 min/wk, n = 16	-0.31 (2.49)	0.33	-5.47 (8.24)	0.91	-0.16 (0.09)	0.81
≥ 120 min/wk, n = 20	-3.12 (2.13)		-6.79 (7.37)		-0.19 (0.08)	
Change in pedometer steps [†]						
<1 mile/d, n = 22	-0.02 (1.98)	0.20	-4.29 (7.01)	0.67	-0.13 (0.07)	0.38
≥ 1 mile/d, n = 14	-4.09 (2.43)		-9.20 (8.81)		-0.24 (0.09)	

NOTE: Data were adjusted for baseline level.

*Adherence was determined from daily activity logs kept for each week of the 6-month study. Women reported the type and duration of every moderate- to vigorous-intensity recreational activity performed daily with adherence defined as average minute per week.

[†] Women wore pedometers for 7 consecutive days at baseline and 6 months. Average steps per day at baseline and 6 months, and the change in average steps per day between baseline and 6 months, were calculated. 1 mile = 1,760 steps.

Table 4. Stratified analysis of change in insulin, IGF-I, and IGFBP-3 [mean (SE)]

	Δ Insulin	<i>P</i>	Δ IGF-I	<i>P</i>	Δ IGFBP-3	<i>P</i>
Age <56 y						
Exercisers, <i>n</i> = 19	0.51 (3.41)	0.50	-0.64 (7.65)	0.20	-0.05 (0.08)	0.24
Controls, <i>n</i> = 15	4.06 (3.86)		14.99 (8.66)		0.11 (0.10)	
Age \geq 56 y						
Exercisers, <i>n</i> = 17	-4.51 (2.81)	0.057	-14.84 (9.33)	0.064	-0.36 (0.13)	0.0047
Controls, <i>n</i> = 17	3.38 (2.81)		10.65 (9.33)		0.20 (0.13)	
		0.53*		0.60*		0.22*
BMI <30 kg/m ²						
Exercisers, <i>n</i> = 16	1.89 (4.60)	0.57	-12.81 (9.62)	0.017	-0.14 (0.12)	0.0070
Controls, <i>n</i> = 20	5.55 (4.06)		19.70 (8.59)		0.34 (0.11)	
BMI \geq 30 kg/m ²						
Exercisers, <i>n</i> = 20	-4.49 (2.06)	0.18	-2.49 (7.39)	0.83	-0.23 (0.10)	0.78
Controls, <i>n</i> = 12	0.23 (2.67)		0.18 (9.55)		-0.18 (0.13)	
		0.40*		0.098*		0.062*
No change or increased % body fat						
Exercisers, <i>n</i> = 12	-3.36 (3.29)	0.17	-7.37 (7.10)	0.0045	-0.27 (0.09)	0.0049
Controls, <i>n</i> = 20	4.70 (4.59)		30.11 (10.04)		0.21 (0.13)	
Decreased % body fat						
Exercisers, <i>n</i> = 24	-2.16 (3.30)	0.59	-5.37 (10.38)	0.63	-0.02 (0.15)	0.53
Controls, <i>n</i> = 12	2.19 (2.62)		1.07 (8.03)		0.10 (0.12)	
		0.25*		0.11*		0.16*
Breast cancer stage 0 or I						
Exercisers, <i>n</i> = 24	-3.17 (2.31)	0.27	5.71 (6.88)	0.30	-0.19 (0.11)	0.012
Controls, <i>n</i> = 12	1.25 (3.21)		18.34 (9.75)		0.31 (0.15)	
Breast cancer stage II or III						
Exercisers, <i>n</i> = 12	2.65 (4.72)	0.85	-30.54 (10.56)	0.0080	-0.20 (0.13)	0.16
Controls, <i>n</i> = 20	3.83 (3.70)		7.53 (8.18)		0.04 (0.10)	
		0.34*		0.15*		0.37*
Hormone therapy						
None						
Exercisers, <i>n</i> = 15	-2.72 (2.54)	0.16	-7.78 (9.99)	0.024	-0.21 (0.14)	0.0063
Controls, <i>n</i> = 9	3.34 (3.28)		34.20 (13.18)		0.52 (0.18)	
Tamoxifen						
Exercisers, <i>n</i> = 11	-5.85 (3.60)	0.29	6.41 (9.53)	0.80	-0.25 (0.11)	0.26
Controls, <i>n</i> = 8	0.07 (4.02)		2.58 (11.18)		-0.05 (0.13)	
Aromatase inhibitors						
Exercisers, <i>n</i> = 10	4.83 (5.62)	0.99	-22.90 (10.42)	0.044	-0.14 (0.15)	0.34
Controls, <i>n</i> = 15	4.79 (4.72)		5.88 (8.51)		0.05 (0.12)	
		0.48*		0.64*		0.25*

**P* for interaction.

IGF in older women may partially be due to the natural decline in concentrations of these hormones with age. Larger, appropriately powered, studies are necessary to confirm the effect of aerobic and/or strength training exercise on insulin and IGF levels in breast cancer survivors. Special emphasis should be placed on the potential interaction of age and BMI.

An important finding of our study was the decrease in IGFBP-3 observed among exercisers. Comparison with the existing literature is difficult given the inconsistent results of previous studies. Although few studies have directly assessed breast cancer prognosis, a study by Goodwin and colleagues found that high levels of IGFBP-3 predicted distant recurrence of breast cancer in postmenopausal women (18). Tissue analysis also showed high levels of IGFBP-3 in breast tumors associated with poor prognosis (34). These results conflict, however, with earlier studies that reported a decreased risk of breast cancer associated with high levels of IGFBP-3 (35). Future studies need to examine the relationships among exercise, IGFBP-3, and breast cancer outcomes.

Although we did not observe stronger effects of exercise on insulin or IGF by weight or body fat loss, it

has been proposed that changes in body fat mediate or modify the change in insulin and IGF associated with increased physical activity. Our study was not appropriately powered to observe effects of exercise on insulin and IGF stratified by weight or body fat change. Future studies need to address this critical question about whether exercise has independent effects on insulin and IGF or is mediated by changes in body fat. Several possible mechanisms may explain exercise-induced decreases in insulin and IGF independent of changes in body fat, including increased postreceptor insulin signaling, increased glucose transporter protein and mRNA, decreased release and increased clearance of free fatty acids, increased muscle glucose delivery, and changes in muscle composition favoring increased glucose disposal (36). Given that high insulin levels promote the synthesis and activity of IGF-I via increases in insulin-mediated changes in IGFBP-3 concentrations, decreases in insulin would favorably influence IGF levels.

The YES study improves upon prior research in several ways. To observe a maximal effect from the exercise intervention, physically inactive women were recruited for this study. The supervised exercise program allowed for improved participant education on how to

exercise safely and at the appropriate intensity. Importantly, it also provided the ability to monitor adherence to the intervention and reduced potential bias by self-report. Other strengths of the YES study include a population-based recruitment strategy, randomization to study groups, a physical activity prescription that met national guidelines, and long study duration. Our sample size is comparable with the earlier studies in breast cancer survivors; however, it is still small in absolute terms, with implications for compromised statistical power overall and with regard to some of our stratified analyses. Additional limitations of the YES study include a single hormone measurement used for the baseline and 6-month assessments, which may have resulted in misclassification of some participants. Also, as baseline and 6-month hormone specimens were assayed together to reduce variability, only those women with both samples were included in the analysis, resulting in the exclusion of seven women. Last, our sample was highly educated and mostly non-Hispanic white. However, the 75 women enrolled in the study did not differ with regard to age, race, or educational status from the nonparticipants that comprised the majority of women diagnosed with breast cancer at Yale-New Haven Hospital in 2004 and 2005.

Conclusions. As evidence accumulates for an association between high levels of insulin, and potentially IGF-I and IGFBP-3, and breast cancer risk and/or death, it becomes increasingly important to identify modifiable factors that decrease insulin and IGF levels. The responsiveness of insulin and IGF to lifestyle changes is key to novel strategies for improving prognosis. Physical activity is a modifiable behavior with a multitude of health benefits, including most recently a favorable association with breast cancer survival (7-9). The results of the YES study show that the recommended level of moderate-intensity aerobic exercise, 30 minutes on 5 days per week, is well tolerated in breast cancer survivors and efficacious in decreasing levels of IGF-I and IGFBP-3. Repetition of this trial with a larger sample size is necessary to confirm this finding. Furthermore, given the four studies, including our own, that have examined the effects of exercise on insulin levels in breast cancer survivors have all been small-scale trials (<100 participants), a larger-scale trial is necessary. Such a trial would help determine whether exercise after a diagnosis of breast cancer has clinically meaningful effects on insulin and other biological mechanisms that may mediate the observed association between physical activity and survival.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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