Effects of a 9-Month Strength Training Intervention on Insulin, Insulin-like Growth Factor (IGF)-I, IGF-binding Protein (IGFBP)-1, and IGFBP-3 in 30–50-Year-Old Women[1]

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Abstract

We assessed the effects of twice weekly strength training on several proposed risk factors for breast and colon cancer: body fat, waist circumference, fasting insulin, fasting glucose, insulin-like growth factor I (IGF-I), and several IGF-binding proteins. Fifty-four healthy women, 30–50 years old, were randomized to no-contact control or treatment: 15 weeks of supervised strength training followed by 6 months of unsupervised training. Fifteen-week changes included reductions in percentage of body fat, fasting insulin, fasting glucose, and IGF-I that were larger in the treatment than control participants (treatment *versus* control mean ± SE: % body fat −1.97 ± 0.42 *versus* −0.43 ± 0.40, $P = 0.01$; insulin (uU/ml) −0.29 ± 0.35 *versus* 0.81 ± 0.38, $P = 0.055$; glucose (mg/dl) −1.92 ± 1.27 *versus* 1.21 ± 1.36, $P = 0.13$; and IGF-I (ng/ml) −30.47 ± 9.75 *versus* 5.86 ± 10.44, $P = 0.02$). There was no treatment effect on IGF-binding proteins 1 and 3 or either of two surrogate measures of free IGF-I. By 39 weeks changes in percentages of body fat were largely maintained; IGF-I returned to baseline levels in the treatment group but remained 15% lower in treatment compared with control participants. Strength training produced favorable changes in several proposed cancer risk factors. The importance of these changes to long-term cancer prognosis, diagnosis, and/or recurrence remains to be determined.

Introduction

Some, but not all, epidemiological studies link physical activity to decreased risk for breast cancer (1). There is more consistent epidemiological evidence of a role for physical activity in reducing risk for colon cancer (1). For both cancers, the mechanisms by which physical activity may confer protection are poorly understood. To untangle the inconsistent findings regarding the role of physical activity in cancer etiology, it is important that we improve our understanding of the link between physical activity and the proposed mechanisms through which it may influence cancer diagnosis, prognosis, and/or recurrence.

One intriguing mechanistic hypothesis links physical activity induced changes in body fat, especially intra-abdominal fat, with changes in insulin and insulin sensitivity, as well as the IGF[3] axis (2). Insulin promotes cellular growth in normal and malignant breast and colon tissues (3–8). A recent prospective cohort study of 508 premenopausal women who underwent treatment for operable breast cancer indicates that obesity and associated elevated fasting insulin levels are associated with distant recurrence and death (9). Insulin plays a role in the IGF axis. IGF-I is a known mitogen that promotes cellular proliferation, differentiation, transformation, and prevents apoptosis (10). IGF-I is directly correlated with mammographic breast density (11), an independent risk factor for development of breast cancer. IGF-I activity is primarily mediated through interaction with the type 1 IGF receptor, a tyrosine kinase receptor with known homology to the insulin receptor (12). IGF-I exerts these effects on normal as well as precancerous and cancerous breast and colon tissue cells (13, 14). Furthermore, transgenic mice that overexpress the IGF-I gene have increased rates of spontaneous or induced tumor formation (15, 16). Mice that overexpress IGF-I have a failure of postlactational involution and enhanced tumorigenesis in the breast (17, 18).

IGF-I has six binding proteins (IGFBPs 1 through 6) that function, in part, to bind >95% of circulating IGF-I, thereby modulating the availability of free IGF-I to act at its receptor (10, 12). Laboratory and population-based research indicates that insulin may partially regulate IGF-I action through the regulation of IGFBP synthesis (19). Overweight individuals, in particular, those with excessive intra-abdominal weight, are at higher risk for hyperinsulinemia (20, 21). Hyperinsulinemia may lead to decreased hepatic synthesis of IGFBP-1 and IGFBP-2 (22, 23), which may translate to increased levels of bioavailable IGF-I, without change in serum total IGF-I levels (19, 22, 23). In a recent cross-sectional study of 400 pre- and postmenopausal women, BMI was not correlated with total IGF-I levels; however, BMI was significantly associated with decreased IGFBP-1 and IGFBP-2 and hyperinsulinemia, indicating that insulin and body fat may mediate bioavailability of IGF-I via its binding proteins (24). Additionally, another cross-

[3] The abbreviations used are: IGF, insulin-like growth factor; IGFBP, IGF-binding protein; BMI, body mass index; HRT, hormone replacement therapy.

sectional study of 225 premenopausal women reported that lean body shape, as assessed by lower BMI, was associated with higher concentrations of IGFBP-1 and IGFBP-2 (25).

Regular strength training has been shown to decrease body fat (26), perhaps from preferential loss of intra-abdominal stores, as well as increase muscle mass (27–29), translating to decreased percentage of body fat. Strength training also improves glucose tolerance and insulin sensitivity (27–29). By contrast, the effects of strength training-induced changes in insulin and body composition on IGF axis hormones are not well understood (10). Sedentary and overweight women may have a growth environment that enhances neoplastic tissue progression in a manner that influences breast and colon cancer diagnosis, prognosis, and/or recurrence. We hypothesized that a progressive strength training program could favorably affect this environment. To test this hypothesis, we conducted a randomized controlled trial of twice weekly strength training in healthy women ages 30–50 and assessed the effects of this intervention on several proposed risk factors for carcinogenesis: body fat, waist circumference, fasting insulin, total IGF-I, several IGFBPs, and residual IGF-I values remaining after regression on binding proteins. These residuals were considered a surrogate measure of bioavailable IGF-I in the absence of measured free IGF-I.

Subjects and Methods

Participant Recruitment and Retention. During December 1999 and January 2000, 60 women ages 30–50 years were recruited from female faculty, staff, and students at the University of Minnesota. An advertisement was placed in the campus paper, and flyers were placed around campus and mailed to a random sample of 3000 30–50-year-old women staff, faculty, and students. Over 700 phone, mail, and e-mail inquiries were received. After hearing a short description of the study, 370 women chose to complete the phone eligibility screening survey. Of those 370, 27% ($n = 101$) were ineligible, 56% ($n = 209$) were eligible but opted not to participate, and 12% ($n = 60$) consented to participate. Women were screened for the following inclusion criteria: self-reported BMI between 20 and 35 kg/m^2; no plans to leave the area for a month or more during the intervention; no recent or ongoing changes in hormonal status that might affect the outcome of the study (pregnant within the past 6 months, lactating within the past 2 months, planning to become pregnant during the study); if premenopausal, consistently taking or not taking hormonal contraception for at least the last 6 months and committed to not making a change in hormonal contraception use during the 9 months of the study; if postmenopausal, consistently taking or not taking HRT for at least the last 6 months and committed to not making a change in use of HRT during the 9 months of the study; no body weight changes ≥10% over the past year; no uncontrolled hypertension (systolic ≤140, diastolic ≤90 mmHg); nonsmokers; no heart disease or other significant medical conditions, including diabetes mellitus or cancer within the past 5 years; no positive responses on the Physical Activity Readiness Questionnaire, a questionnaire designed to identify persons for whom increased physical activity may be contraindicated (30); no prescription medications expected to alter the results of the study (including cholesterol lowering medications, psychiatric medications taken at dosages expected to affect weight, appetite suppressants, or thyroid medications); no conditions that might inhibit the ability to participate in strength training (including muscle injuries, orthopedic problems, motion limiting osteoarthritis, or fibromayalgia); no

health conditions that affect metabolic rate (such as thyroid disease); sedentary to moderately physically active (up to three times a week of physical activity and up to moderate intensity); no strength training during the past year; and no past strength training of two or more times a week for 6 months or longer. Randomization was stratified by decade of age (30–39 *versus* 40–50) because of concern regarding possible effects of perimenopausal hormonal changes on the outcomes of interest. Two women each in the treatment and control groups reported being postmenopausal at baseline; all four reported taking HRT for >6 months.

Three women dropped out of the study for personal reasons: two women in the control group and one in the treatment group. We had incomplete blood samples for two women (one treatment, one control). In addition, one treatment group participant was diagnosed with Grave's disease 1 month before study completion. Results for these 6 participants are excluded from all analyses. Results presented in this paper are for the remaining 54 women who successfully completed the study. No new injuries were incurred in the treatment group beyond expected muscle strain and soreness. The study protocol was reviewed by and followed all regulations of the University of Minnesota Institutional Review Board for the protection of human subjects in research. Participants received $200 for successful study completion. Access to the intervention exercise facility and professionally certified fitness trainers was paid for by the study grant, although parking was not paid for.

Intervention. All participants, regardless of group assignment, were asked to avoid changes in their dietary habits for the purpose of weight change, for the duration of the study; seasonal variations in diet were allowed. Participants who at baseline reported current participation in some form of low-intensity aerobic or stretching exercise (most commonly 1–2 weekly walks) were asked to continue those activities at the same level for the entire duration of the intervention, regardless of group assignment.

The treatment group was enrolled in a 50-min strength training class held twice weekly for 15 weeks at the University of Minnesota Recreation Center (Minneapolis, MN). At each session, participants performed three sets each of nine common strength training exercises; participants lifted as much weight as they could for 8–10 repetitions/set. The nine strength training exercises included exercises performed on Cybex strength training equipment (Smith press squats, leg press, leg extension, seated leg curl, lat pulldowns) and with free weights (bench press, overhead press, bicep curls, and tricep kickbacks). Through the first 15 weeks of the intervention, participants were instructed to progressively increase the weight of a given exercise by the smallest increment possible after two sessions of lifting the same weight and completing 10 repetitions for all three sets.

At the end of the 15-week class, treatment group participants were provided with a 6-month membership to the same exercise facility. Participants performed this unsupervised maintenance portion of the strength training intervention on their own, or if they chose, with a partner. They were instructed to continue performing at least two or, if they preferred, three sets of all nine strength training exercises, maintaining at least the same or higher weight load as lifted during the last week of the 15-week class. Participants maintained exercise session logs in which they recorded information about number of sets and the weight load for each exercise performed per strength training session. These logs were reviewed twice-weekly by study staff to track participant attendance and progress. Participants

who missed sessions were contacted by telephone or e-mail to encourage them to complete the missing session. During the 15-week supervised intervention, 92% of prescribed exercise sessions were completed. During the following 6 months of unsupervised exercise, 83% of the prescribed exercise sessions were completed. Strength changes from baseline to 15 and 39 weeks corroborated self-reported adherence data as the treatment group showed increases of 19 and 24% for bench press and 13 and 20% for leg press over 15 and 39 weeks, respectively ($P < 0.0001$ for bench press, $P < 0.004$ for leg press when compared with the control group). The control group participated in measurements only.

Measurements. All measurements described below were taken at a measurement visit that took place at the University of Minnesota General Clinical Research Center (Minneapolis, MN). These visits occurred at three time points: baseline, 15 weeks, and 39 weeks. All measurement data were double-entered by study staff into a data management program. Participants were asked to refrain from physical activity for 48 h before each measurement visit. Body weight and height measurements, blood draws, and dual X-ray absorptiometry (for body composition) were performed by clinical research nurses, blinded to treatment group status, between 6:30 and 9:30 a.m., after a 12-hour fast, and between 5 and 11 days after the start of menstrual flow for menstruating participants. Participants were asked to empty their bladder and change into a hospital gown before all measurements. Body mass was measured on a digital scale and stature was assessed using a mounted stadiometer, both calibrated daily (Scale-tronix 5005 stand-on digital scale; Scale-tronix, White Plains, NY). Waist circumference, at the level of the umbilicus, was measured in duplicate by the same researcher for all measurements; the mean was used for analysis. Body composition was measured on the Lunar Prodigy Dual X-ray Absorptiometer (software version 2.15; Lunar Radiation Corporation, Madison, WI), calibrated monthly with daily checks to ensure calibration was maintained. Body fat percentage is expressed as percentage of non-bone tissue that was fat.

Fasting blood glucose was measured by clinical research nurses blinded to treatment group status at bedside with a Beckman glucose analyzer at the University of Minnesota General Clinical Research Center. Interassay coefficients of variability for glucose were 7.9, 8.6, and 8.8% at baseline, 15 weeks, and 39 weeks, respectively. Serum samples were stored at $-70°C$, then sent at study completion to reference laboratories for completion of insulin and IGF axis assays. Random samples were sent in duplicate to be tested for variation; the labs were blinded to which samples were sent in duplicate. Fasting serum insulin levels were measured by a two-site immunoenzymatic assay at the Mayo Clinic (Rochester, MN). Intra- and interassay coefficients of variability were <2.6 and $<4.6\%$, respectively. ELISAs of IGF-I, IGFBP-1, and IGFBP-3 were performed at the reference labs of Diagnostic Systems Laboratories (Webster, TX). Samples were run with two standard controls included in the kit for each analyte. The sensitivities for the assays for IGF-I, IGFBP-1, and IGFBP-3 were 0.03 ng/ml, 0.04 ng/ml, and 0.25 ng/ml, respectively. The intra- and interassay coefficients of variation for IGF-I were 6.5% at 169.67 ng/ml and 4.8% at 132.61 ng/ml, respectively; for IGFBP-1, they were 2.5% at 31.16 ng/ml and 6.8% at 30.48 ng/ml, respectively; and for IGFBP-3, they were 7.3% at 74.40 ng/ml and 8.2% at 65.55 ng/ml, respectively. Except for glucose, all blood assays were performed in duplicate with the mean used for analysis. For all assays, technicians were blinded to treatment status but did match reagent batch to measurement time point for all participant ID numbers. For example, assays for the baseline time point were performed in a single batch for all participants.

Upper and lower body strength were assessed by one repetition maximum tests for the bench press and leg press in two additional clinic visits that occurred 48 h apart and were supervised by trained research staff. At 15 and 39 weeks, up to 4 women in each group failed to complete the bench press and or leg press strength tests. Fear of exacerbating preexisting injuries was the most common reason provided for not completing the strength tests.

In addition to physiological measurements, participants also completed three surveys (described below) at measurement visits: the Typical Weekly Physical Activity Survey, 4-day food records, and a demographic survey (given at the baseline measurement visit, only). The Typical Weekly Physical Activity Survey, used here to assess participant physical activity outside of the strength training protocol, was designed to assess multiple domains of physical activity in women (31).

Reliability and validity assessment of this survey was conducted on 160 white, black, and Native American women. The intraclass correlation coefficient for repeated measures of total physical activity with the Typical Weekly Physical Activity Survey was 0.51. Correlations of the Typical Weekly Physical Activity Survey score with physical activity record, body fat percentage, maximal aerobic power, and accelerometer were 0.40, -0.09, 0.25, and 0.40, respectively. These correlations compare favorably with other well-accepted and commonly used physical activity surveys (32). The units for the total physical activity score are metabolic equivalent minutes/day (MET $min^{-1} \times day^{-1}$), which includes both duration and intensity components. A registered dietician, blinded to treatment status, entered the 4-day food records into the Nutrition Data System software (version 4.02   30; Minnesota Nutritional Coding Center, Minneapolis, MN), which allowed for determination of total energy intake and percentage of energy from fat. The demographic survey included questions regarding age, ethnicity, marital status, and educational history.

Statistical Analysis. Statistical analyses were conducted with SAS version 6.12. Baseline characteristics between groups were compared by two-sided t tests for continuous variables and χ^2 tests for categorical variables. Baseline comparisons of body size variables, physical activity, and energy intake were made with two-sided t tests. Fifteen- and 39-week changes in body size variables, physical activity, and energy intake were compared across treatment status with means from regression models adjusted for the baseline value of the dependent variable. Baseline serum hormone and glucose levels were compared across treatment status with means from regression models adjusted for baseline levels of body fat, lean mass, age, physical activity, and energy intake. Fifteen- and 39-week changes in serum hormone and glucose levels were compared across treatment status with means from regression models adjusted for baseline levels of the dependent variable and baseline levels of body fat, lean mass, age, physical activity, and energy intake. Replacement of baseline energy intake and energy expenditure variables with changes in energy intake and physical activity in models predicting 15- or 39-week changes in serum hormones and glucose did not alter the findings presented.

To estimate bioavailable IGF-I levels and the effects of the intervention on these levels, we predicted IGFBP-1 and IGFBP-3 from total IGF-I levels and output the residuals. This residual approach was preferred over the more commonly used

	Control ($n = 27$)	Treatment ($n = 27$)	
Table 1 Baseline demographic characteristics			
Variable	Mean (SD) or % (n)	Mean (SD) or % (n)	P^a
Age	42 (6)	41 (6)	0.66
BMI (kg/m^2)	27.0 (4.3)	25.4 (4.3)	0.18
% Caucasian	89 (24)	93 (25)	0.64
% married	74 (20)	67 (18)	0.55
% completed college	88 (24)	81 (22)	0.44

^{a} P from two-sided t test for continuous variables, χ^2 for all categorical variables.

ratio of IGF-I with binding proteins because the use of a ratio requires an assumption of a slope of one. Repetition of these analyses after excluding participants who were taking HRT or hormonal contraception did not alter the results presented.

Results

Table 1 provides demographic data comparing the treatment and control groups at baseline. The participants of this study were mostly married, college educated, and Caucasian. The mean BMI (kg/m^2) in each group shows that on average, the participants fell into the public health category of overweight but not obese (defined as BMI between 25 and 29.99; Ref. 33).

We noted differences between the treatment and control groups at baseline for body weight, waist circumference, total body fat, and energy intake. Some, but not all of these differences, were statistically significant. The treatment and control group distributions of each of these variables nearly completely overlapped. A few women in the control group who were outliers with regard to body fat explain these baseline differences. Exclusion of these women from the analyses did not alter the reported findings.

Table 2 shows the mean and SD by treatment status for body size variables, physical activity (outside of strength training), dietary intake, insulin, total IGF-I, IGFBP-1, IGFBP-3, and the residuals of IGF-I from models predicting IGFBP-1 and IGFBP-3 from total IGF-I. Values for these variables are given for baseline, as well as the changes in these variables from baseline to 15 weeks (the length of the supervised intervention) and from baseline to 39 weeks (the length of the supervised plus the unsupervised intervention). Figs. 1 through 4 show the mean levels (with SE bars) for insulin, total IGF-I, IGFBP-1, and IGFBP-3 at baseline, week 15, and week 39 for the treatment and control groups. The values in Figs. 1–4 are means from regression models adjusted for baseline age, body fat, lean mass, physical activity, and energy intake.

We observed a 12% decrease in total IGF-I resultant to a 15-week progressive strength training program in previously untrained middle-aged women. At the end of this 15 week intervention, IGF-I levels in the treatment group were 21% lower than in the control group. This statistically significant strength training induced decrease in total IGF-I occurred concurrently with decreases in percentage of body fat, total body fat (kg), and fasting glucose, as well as increases in lean mass (kg). There was no evidence of any treatment effect on IGFBP-1 or IGFBP-3 or the residual IGF-I values we used as surrogates for bioavailable IGF-I. There was a small, marginally statistically significant between group difference in the 15-week change in insulin. The treatment-induced changes in body fat and lean mass were largely maintained (especially in comparison to changes in the control group) over the additional 6 months of unsupervised strength training. During this strength training maintenance phase, total IGF-I increased to slightly

above baseline levels in the treatment group, although it remained 15% lower in treatment than control participants by 39 weeks.

Discussion

We chose strength training rather than aerobic exercise for this intervention for several reasons. First, we were interested in the effects of exercise independent of changes in body weight, as there is documented evidence that IGF-I is inversely associated with BMI (10). Second, strength training has been shown to have positive effects on insulin and insulin sensitivity (27, 29, 34), perhaps translating to a favorable effect on the IGF axis. Third, benefits from strength training can be obtained with two exercise sessions/week, compared with a common prescription of three to five moderate intensity aerobic exercise sessions. Fewer weekly sessions may improve adherence. As described above, participants completed 92% of all prescribed sessions over the first 15 weeks and 83% in the following 6 months. In comparison, adherence to programs that prescribe 5 weekly walks is closer to 75% over a similar time period (35).

The improvements in lean mass and body fat observed in this study are consistent with observations from prior randomized controlled trials that have reported decreased body fat and increased lean body mass after several months of strength training in untrained young women (36, 37) and older adults (28, 38–42). Prior randomized controlled trials have consistently reported improved glucose tolerance and/or insulin sensitivity resulting from strength training (27, 29, 34). Similarly, in our results, changes in fasting glucose and insulin over 15 and 39 weeks were more favorable in the treatment than the control group. However, only the comparison of 15-week changes for insulin approached statistical significance, and all of the observed changes were small.

Ours is one of the few intervention trials to report reductions in total IGF-I or its binding proteins after 15 weeks of progressive supervised strength training. Strength training intervention studies in older men and women have reported total IGF-I changes ranging from a small decrease (43), maintenance (44), less of an increase in treatment than control participants (45), or the same amount of increase in treatment and control participants (46). Similar to our findings, these studies in older adults have generally reported concurrent decreases in body fat (43–46). In young, lean, healthy, and exercise trained populations, most (47–50) but not all (51) strength training intervention studies report increases in total and or free IGF-I of 20–25%. In contrast to our findings and those from studies of older adults, the only study in younger subjects that measured body fat reported no change (49). A recent review noted that inconsistent findings with regard to physical activity effects on IGF axis hormones may be age related (10). Two other variables to consider in the study populations for these prior studies include baseline body fat and training status. Our findings in middle aged, untrained women are more consistent with the result of prior interventions in older, untrained, and/or overweight adults. Perhaps the effect of strength training on IGF axis hormones is distinct according to baseline body fat, training status, and/or age.

There is evidence that the subpopulation that might experience the greatest health-related benefits from an increase in physical activity are those who are most sedentary (52). For example, the effects of physical activity on insulin sensitivity and glucose tolerance have been observed to be greater in those who are at higher initial risk for diabetes compared with those at lower risk (21, 34). In our data, treatment group women who

Table 2   Body size, insulin, glucose, and IGF axis variables at baseline and changes over 15 and 39 weeks (mean ± SE)

Variables	Baseline			Change from baseline to 15 weeks			Change from baseline to 39 weeks		
	Control	Treatment	P^a	Control	Treatment	P^a	Control	Treatment	P^a
Weight (kg)	74.6 ± 2.60	68.2 ± 2.15	0.06	0.49 ± 0.35	0.54 ± 0.36	0.92	0.28 ± 0.59	0.33 ± 0.59	0.95
Body fat %	40.7 ± 0.12	38.4 ± 0.13	0.2	−0.43 ± 0.40	−1.97 ± 0.42	0.01	−0.41 ± 0.49	−1.86 ± 0.49	0.04
Total energy intake (kjoules)	7178 ± 384	8236 ± 295	0.03	−44 ± 71	−78 ± 66	0.73	85 ± 96	−10 ± 80	0.46
Total physical activity (MET min^{-1} × day^{-1})	1663 ± 91	1524 ± 75	0.24	161 ± 115	268 ± 115	0.51	156 ± 66	56 ± 66	0.29
Total lean (kg)	41.8 ± 1.02	39.6 ± 0.87	0.1	0.54 ± 0.34	1.44 ± 0.25	0.01	0.44 ± 0.26	1.34 ± 0.26	0.02
Total fat (kg)	29.8 ± 1.89	25.5 ± 1.52	0.08	−0.06 ± 0.29	−0.88 ± 0.30	0.06	−0.04 ± 0.43	−0.83 ± 0.43	0.21
Waist circ. (cm)	95.1 ± 2.58	88.5 ± 2.11	0.05	1.06 ± 0.50	−0.04 ± 0.50	0.13	2.07 ± 0.70	1.28 ± 0.70	0.43
Insulin (uU/ml)	4.46 ± 0.59	5.18 ± 0.54	0.42	0.81 ± 0.38	−0.29 ± 0.35	0.055	1.16 ± 0.45	0.05 ± 0.42	0.10
Glucose (mg/dl)	92.1 ± 1.63	90.1 ± 1.50	0.42	1.21 ± 1.36	−1.92 ± 1.27	0.13	−0.36 ± 1.50	−3.55 ± 1.37	0.15
Total IGF-I (ng/ml)	240 ± 12.52	218 ± 11.70	0.24	5.86 ± 10.44	−30.47 ± 9.75	0.02	35.93 ± 11.10	6.50 ± 10.36	0.08
IGFBP-1 (ng/ml)	55.60 ± 7.15	49.52 ± 6.68	0.57	−2.41 ± 5.22	−0.67 ± 4.88	0.82	−6.55 ± 4.46	−10.77 ± 4.17	0.52
IGFBP-3 (ng/ml)	3551 ± 143	3716 ± 133	0.44	−106 ± 103	−45.6 ± 96	0.69	570 ± 179	138 ± 167	0.11
IGF-I residual from IGFBP-1^b (ng/ml)	4.60 ± 7.14	−1.29 ± 6.68	0.58	−0.08 ± 5.10	−0.02 ± 4.76	0.99	3.89 ± 4.37	−3.63 ± 4.08	0.25
IGF-I residual from IGFBP-3^b (ng/ml)	−108 ± 138	105 ± 129	0.30	−0.42 ± 113	−2.90 ± 105	0.99	99.8 ± 154	−63.6 ± 144	0.48

[a] Baseline comparisons of body size variables, physical activity, and energy intake are from two-sided *t* tests. Between group comparisons of 15 and 39 week changes for body size, physical activity, and energy intake variables are means from regression models adjusted for baseline levels of the dependent variable. Baseline comparisons of serum hormone and glucose levels are means from regression models adjusted for baseline levels of age, body fat, lean mass, energy intake, and physical activity. Between group comparisons of changes in serum hormone and glucose levels over 15 and 39 weeks are means from regression models adjusted for baseline levels of the dependent variable, as well as baseline levels of age, body fat, lean mass, energy intake, and physical activity.
[b] IGFBP-1 and IGFBP-3 were predicted from IGF-I in two separate linear regression models. The residuals were output as a surrogate for bioavailable IGF-I.
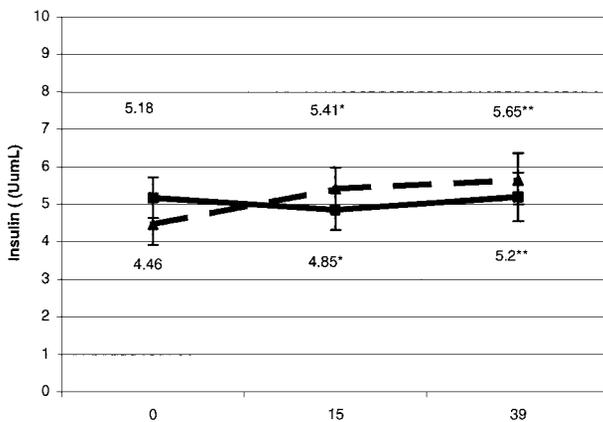

Fig. 1. Fasting serum insulin at baseline, 15, and 39 weeks by treatment status. Values at each time point are adjusted for baseline age, body fat, lean mass, physical activity, and energy intake. *, between-group differences, *P* = 0.055; **, between-group differences, *P* = 0.1.

Fig. 2. Fasting serum IGF-1 at baseline, 15, and 39 weeks by treatment status. Values at each time point are adjusted for baseline age, body fat, lean mass, physical activity, and energy intake. *, between-group differences, *P* = 0.02; **, between-group differences, *P* = 0.08.

were leaner at baseline experienced larger decreases in body fat and waist circumference, whereas women who had higher body fat percentage at baseline experienced larger decreases in insulin and total IGF-I, as well as larger increases in lean mass (53). These effects according to baseline level of body fat were not as evident at week 39 (data not shown). The lack of maintained change makes it difficult to interpret the meaning of the 15-week differential effects. In addition, our sample sizes were too small to draw any conclusions based on these subset analyses. Future studies should stratify recruitment according to baseline body fat percentage, age, and training status to address these issues more completely.

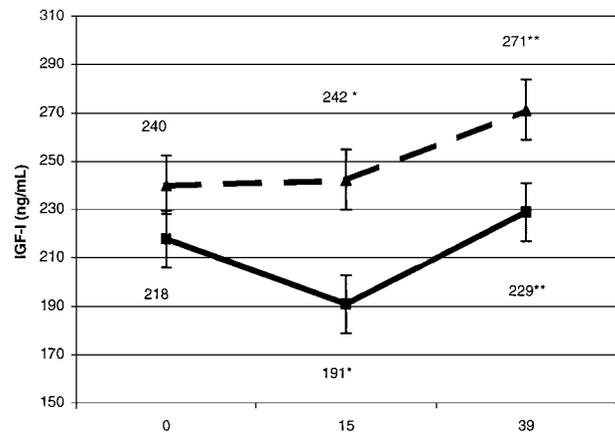The period of active muscle building was likely during the first 15 weeks of the intervention, concurrent with decreased IGF-I levels in the treatment compared with the control group. During weeks 15 to 39, treatment participants maintained but did not experience additional muscle mass increases, concurrent with an increase in IGF-I to slightly above baseline levels. Perhaps IGF-I levels decrease during periods of active muscle building. What we cannot know from these data are whether the treatment group would have experienced larger increases from weeks 15 to 39 if they had stopped strength training during this time period. The control group experienced additional increases in IGF-I from week 15 to 39, with a net result of a 15% lower IGF-I level in treatment compared with control groups by week 39. It is unlikely that the increase in total IGF-I levels observed in the treatment group from week 15 to 39 was attributable to
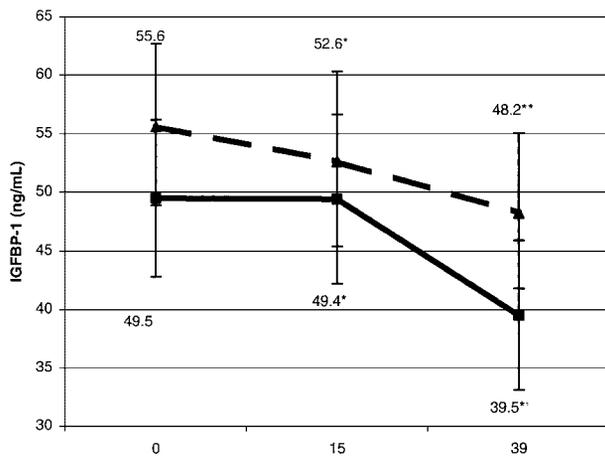
Fig. 3. Fasting serum IGFBP-1 at baseline, 15, and 39 weeks by treatment status. Values at each time point are adjusted for baseline age, body fat, lean mass, physical activity, and energy intake. ∗, between-group differences, $P = 0.82$; ∗∗, between-group differences, $P = 0.52$.

Fig. 4. Fasting serum IGFBP-3 at baseline, 15, and 39 weeks by treatment status. Values at each time point are adjusted for baseline age, body fat, lean mass, physical activity, and energy intake. ∗, between-group differences, $P = 0.69$; ∗∗, between-group differences, $P = 0.11$.

a lack of exercise adherence (average adherence was 83% and muscle strength also improved during weeks 15–39).

The present findings raise some questions. If total IGF-I changes resultant to strength training are temporary, they are less likely to be an important mechanism through which strength training would confer protection from cancer diagnosis, prognosis, and/or recurrence. We observed a 15% between-group difference at 39 weeks that was marginally statistically significant and may or may not have been attributable to the intervention. Furthermore, it is not possible to know from these data whether the 15% difference in serum IGF-I levels between the treatment and control groups at 39 weeks could be maintained long term. To place this 15% change in context: a 20 mg/day dose of tamoxifen has been observed to cause a 16% decrease in IGF-I (54). It would be interesting to determine whether strength training could produce and maintain a 15% difference in serum IGF-I levels in initially sedentary and generally overweight women, as well as whether this effect would have any impact on cancer diagnosis, prognosis, and/or recurrence. It is also possible that an effect of physical activity on cancer diagnosis, prognosis, and/or recurrence is conferred through the more consistently observed changes in body fat, especially visceral fat and glucose/insulin dynamics. These effects may or may not involve the IGF-I axis.

Cross-sectional and prospective observational studies have reported a putative association between IGF axis hormones and cancer risk (14, 55–58). A potential association between physical activity and cancer risk is also observed in epidemiological studies (1). There are too many unanswered questions to determine whether there is a link between these findings. For example, there is observational evidence that IGFBPs or bioavailable IGF-I levels may be as important to cancer risk as total IGF-I levels risk (14, 55–58). The present results do not support the hypothesis that strength training would change IGFBP-1 or IGFBP-3 or free IGF-I in a manner that would mediate the proposed connection of physical activity and cancer. It should be noted that the effects of each binding protein on the bioavailability of IGF-I is unique and may be affected by other factors. For example, the effect of IGFBP-1 on IGF-I activity differs according to phosphorylation status (10). Furthermore, bioavailable IGF-I and its binding proteins have
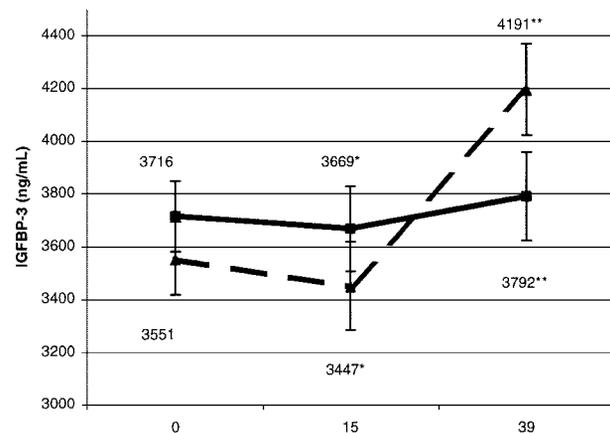
important autocrine and paracrine effects in the breast tissues that cannot be assumed to be consistent with systemic levels (10, 59). However, recent studies in a mouse model system suggest that serum IGF-I levels can regulate colon cancer growth and progression (60), suggesting that systemic levels of total IGF-I can have significant influence on tumor progression. Preliminary data suggest a similar role for serum IGF-I levels in malignant transformation of the mammary gland (61).

This study has several limitations. First, the instruments used to measure changes in energy expenditure and intake were crude in comparison to the quality of the measurements of body size changes. It is possible that some or all of the changes reported herein could be explained by eating or energy expenditure adjustments in reaction to participation in a strength training program. Another limitation of the current study is the combination of a small overall sample size and the inclusion of women who are pre-, peri-, and postmenopausal. Sensitivity analyses did not indicate any differences in the reported effects by decade of age or pre- *versus* postmenopausal status (results not shown). However, the small sample sizes in these subgroups do not allow for full investigation of differential effects according to menopausal status. A third limitation of this study is that the baseline and follow-up samples were assayed in separate batches. Batch-to-batch variability in assays could obscure biological changes. In future studies, each subject's sample should be assayed in the same batch to avoid this limitation. A fourth limitation of this and other intervention studies that have reported changes in total and/or bioavailable IGF-I and binding proteins resultant to strength training is that estrogen and its metabolites were not measured concurrently. These measurements may provide important information in light of the cross-talk between the IGF axis, insulin, estrogen and its metabolites, and estrogen receptors (59). In addition, although it is unclear whether strength or endurance training alters estrogen levels, there has been an observation that physical activity could alter the ratio of estrogen metabolites in a way that may prevent formation of DNA adducts (62). These important issues should be addressed in future research.

In summary, we observed that 15 weeks of strength training resulted in increases in lean mass, as well as decreases in body fat, fasting glucose, and total IGF-I, without notable change in either IGFBP-1 or IGFBP-3 or two surrogate meas-

ures of free IGF-I. Some, but not all, of these changes were maintained to 39 weeks. In the context of prior studies, the results of this study point to the need for additional research on the effects of physical activity on IGF axis variables in groups that are initially sedentary, stratified at baseline by body fat percentage, and with additional measures of estrogen and its metabolites.

Physical activity is a modifiable behavior with a multitude of health benefits (52). We need to better understand the mechanisms that link physical activity with breast and colon cancer risk. Development of efficacious physical activity interventions to prevent cancer and improve cancer prognosis is important to clinicians, researchers, advocates, and survivors alike.

Acknowledgments

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Effects of a 9-Month Strength Training Intervention on Insulin, Insulin-like Growth Factor (IGF)-I, IGF-binding Protein (IGFBP)-1, and IGFBP-3 in 30–50-Year-Old Women

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