Safety and Efficacy of Weight Training in Recent Breast Cancer Survivors to Alter Body Composition, Insulin, and Insulin-Like Growth Factor Axis Proteins

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Abstract

Background: **This randomized controlled trial assessed the safety and effects of twice-weekly weight training among recent breast cancer survivors. Outcomes included body size and biomarkers hypothesized to link exercise and breast cancer risk.**

Methods: **A convenience sample of 85 recent survivors was randomized into immediate and delayed treatment groups. The immediate group trained from months 0 to 12; the delayed treatment group served as a no exercise parallel comparison group from months 0 to 6 and trained from months 7 to 12. Measures at baseline, 6 and 12 months included body weight, height, body fat, lean mass, body fat %, and waist circumference, as well as fasting glucose, insulin, insulin resistance, insulin-like growth factor-I (IGF-I), IGF-II, and IGF-binding protein-1, IGFBP-2, and IGFBP-3. Injury reporting was standardized.**

Results: **The intervention resulted in significant increases in lean mass (0.88 versus 0.02 kg, $P < 0.01$), as well as significant decreases in body fat % (−1.15% versus 0.23%, $P = 0.03$) and IGF-II (−6.23 versus 28.28 ng/mL, $P = 0.02$) comparing immediate with delayed treatment from baseline to 6 months. Within-person changes experienced by delayed treatment group participants during training versus no training were similar. Only one participant experienced a study related injury that prevented continued participation.**

Conclusion: **Twice-weekly weight training is a safe exercise program for recent breast cancer survivors that may result in increased muscle mass, as well as decreased body fat % and IGF-II. The implications of these results on cancer recurrence or survival may become more evident with longer exercise intervention trials among breast cancer survivors.** (Cancer Epidemiol Biomarkers Prev 2005;14(7):1672–80)

Introduction

With over 200,000 diagnoses of breast cancer each year in the United States (1), there is tremendous interest in discovery of a modifiable risk factor for breast cancer. Many but not all observational studies show exercise to be inversely associated with risk for breast cancer (2). However, the mechanisms by which exercise would alter breast cancer risk are not yet fully explicated. Several mechanisms have been proposed, including reduction of excess body weight, excess body fat, elevated fasting insulin, insulin resistance, and alterations in plasma levels of insulin-like growth factor (IGF) axis proteins (2). Each of these variables has been observed to be associated with the development of breast cancer *in vitro*, *in vivo*, and/or in observational studies (3-7). If these factors can be improved by exercise training, they could form part of the biological basis for the purported reduction of breast cancer risk among exercise-trained women.

One population in which it is important to establish that exercise can have positive effects on these hypothesized biomarkers is women at increased risk for breast cancer, including breast cancer survivors. It has been proposed that the secondary prevention research program that used myocardial infarction survivors to explore the effects of exercise on cardiovascular disease risk factors could be used as a model for research using cancer survivors to explore the physiologic effects of exercise training on biomarkers for cancer (8). There has been little research on the effect of exercise on any of the above hypothesized biomarkers among breast cancer survivors.[3]

In addition, breast cancer treatment itself is associated with increases in body fat (9-12), which may translate into hyperinsulinemia and reduced serum IGF-binding proteins. Weight gain after breast cancer diagnosis may be associated with distant recurrence and poorer survival (13). It can be assumed that this post-diagnosis weight gain is largely composed of body fat; there is evidence that the majority of the weight gained during breast cancer treatment is fat (11). Therefore, the extent to which breast cancer survivors can improve body composition, insulin, and IGF axis proteins through an exercise intervention may have implications for recurrence and survival.

The present study was undertaken to assess the effects of a twice-weekly weight training intervention on recent breast cancer survivors (4-36 months post-adjuvant therapy). There were several reasons weight training was chosen over aerobic activity as the mode of physical activity for the intervention. First, weight training has been shown to positively alter the outcomes of interest, including body composition (14), glucose/insulin dynamics (15-17), and IGF axis proteins (18). Second, adherence to exercise interventions is an issue for all populations and we have recently shown the behavioral feasibility of twice-weekly weight training among midlife women who are not cancer survivors (18). Third, a set of secondary aims for this study (to be reported on elsewhere) related to the potential for breast cancer survivors in the ''watchful waiting'' time frame in which we recruited to increase their sense of control over their

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lives through weight training (e.g., psychologic empowerment via physical strength increases). Finally, because weight training alters body composition but does not alter body weight, weight training provides an opportunity for examining the effects of exercise in the absence of weight change.

Body weight was rejected as a primary outcome for this study because weight training is expected to increase lean body mass (a positive outcome) and decrease body fat percentage (also a positive outcome) with little net effect on body weight. Therefore, the primary outcome of interest was change in body fat percentage and lean body mass, as these outcomes more specifically reflect the physiologic changes of importance when body weight is altered. Secondary outcomes included changes in body weight, body mass index (BMI, in kg/m^2), body fat, and waist circumference, as well as fasting glucose, insulin, insulin resistance, and IGF–axis proteins. Furthermore, injuries incurred by participants during the study period were systematically recorded to assess the safety of the intervention for breast cancer survivors.

Materials and Methods

Study Design and Randomization. This study used a partial crossover design, as depicted in Fig. 1. Participants were randomized after baseline measures into the immediate and delayed treatment groups, in a blocked randomization procedure that balanced participants according to both age and baseline body fat percentage. After baseline measures were complete for each recruitment wave, a random number table was used with nonidentifying participant identification numbers to randomly allocate participants into one of two groups within age and baseline body fat percentage groups. The body fat percentage and age groupings were determined by splitting each recruitment wave at the median. The randomization procedure used prevented investigators from influencing treatment allocation. Measurement staff remained blinded until the end of the study, with the exception of the strength testing staff, who used a script to avoid biasing results. The institutional review board of the University of Minnesota and the Park Nicollett Research Foundation approved all study procedures.

Recruitment and Participants. A convenience sample of 86 women was recruited from among breast cancer survivors living in the Greater Minneapolis/St. Paul metropolitan area between October 2001 and June 2002. Participants were recruited in four waves. The immediate treatment groups from waves 1 to 4 started training in January, March, May, and June 2002, respectively. Each recruited wave of women assigned to delayed treatment began weight training after completing the 6-month measurements. Recruiting methods included sending flyers to oncologists in the Twin Cities metropolitan area to request that they make patients aware of the study, visits to breast cancer support groups in the metro area, word of mouth, a presentation to the board of directors of the Twin Cities Affiliate of the Susan G. Komen Foundation, and direct mailings to women who had been treated through two health care systems. Flow of participants through the study is provided in Fig. 2. Reasons for loss to follow-up included breast cancer recurrences ($n = 4$), lack of time ($n = 1$), life events (e.g., divorce, moving out of state; $n = 2$), lack of continued interest in the study ($n = 8$), and in one delayed treatment group participant, a back injury unrelated to the study.

Eligibility requirements included that participants had to have completed all treatment for breast cancer (except for hormonal therapy such as Tamoxifen or an aromatase inhibitor such as Anastrazole) 4 to 36 months before baseline measures. Participants could not have any medical conditions that would prohibit participation in a weight training program. Nor could participants be morbidly obese (BMI > 40 kg/m^2), hypertensive (systolic blood pressure > 160 mm Hg and/or diastolic blood pressure >99 mm Hg), currently on a weight loss plan, planning to start a weight loss plan during the period of the study, planning to move away from the area or be away from area for >3 weeks during study period, pregnant or lactating, or have plans to become pregnant during the study period. If an otherwise eligible participant was planning additional surgery (e.g., reconstruction) during the study period, she was asked to delay study entry until completing that surgery and recovery period. Participants had to be nonsmokers for at least the past 2 years, sedentary to moderately physically active (no more than three sessions per week of no more than moderate

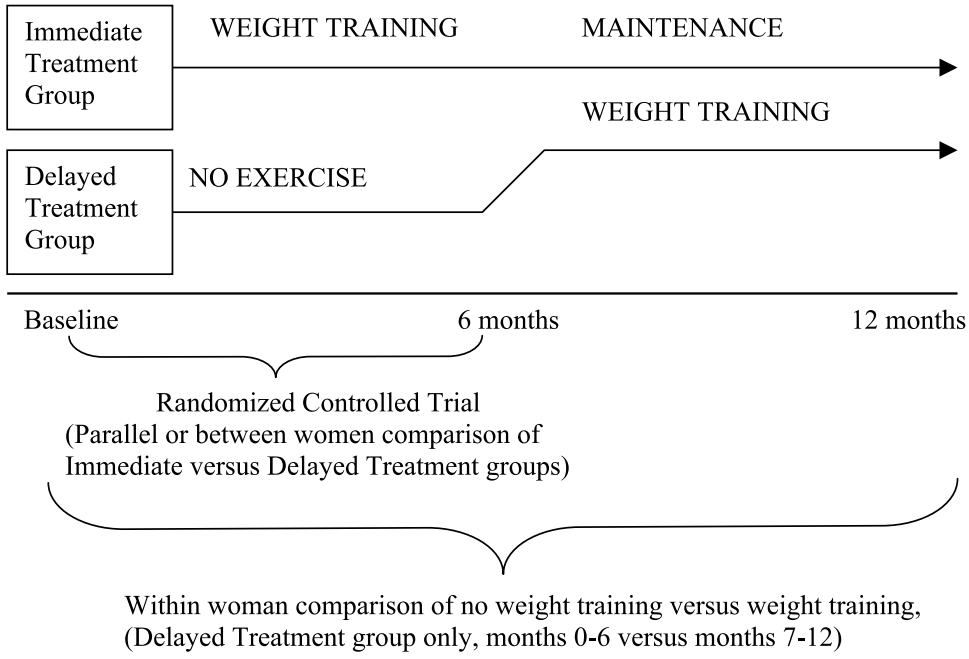

Figure 1. Study design.

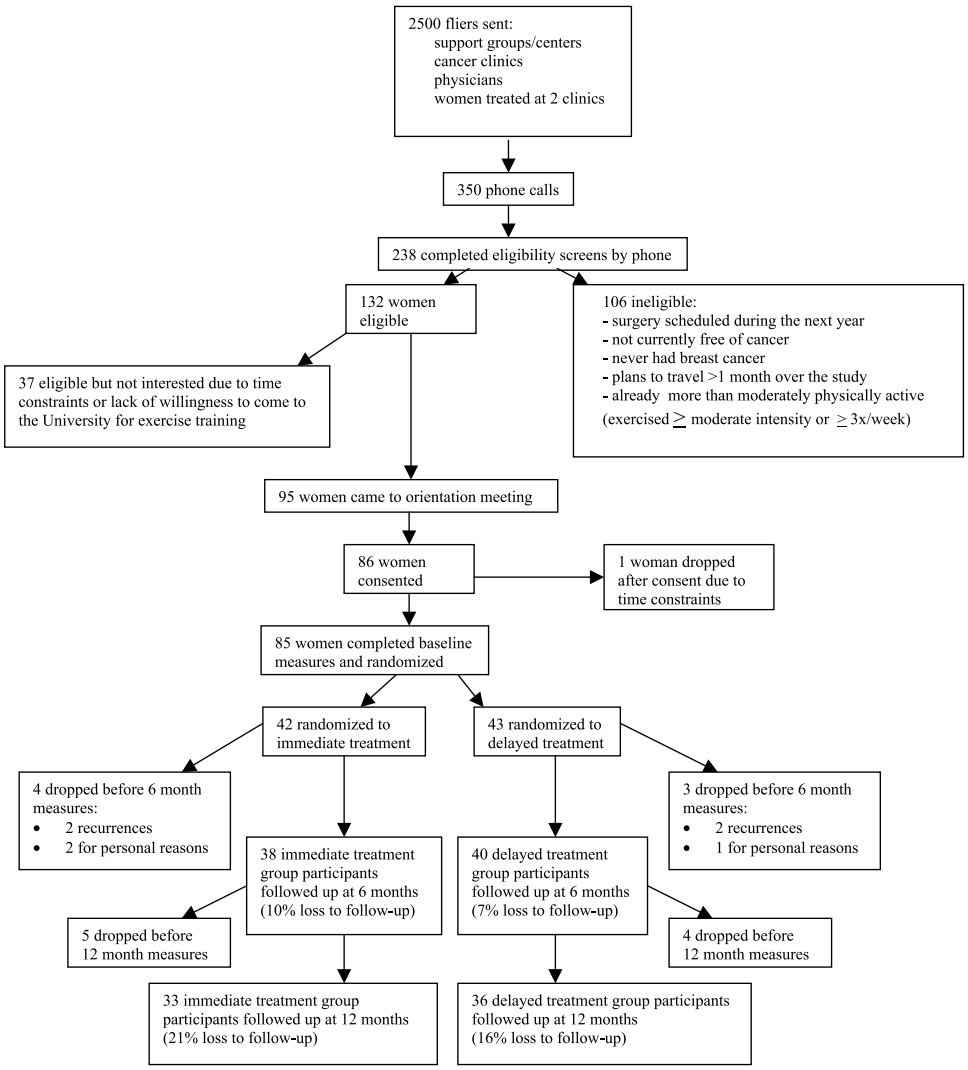

Figure 2. Flow of participants through the study.

intensity activity, no weight training history), and body weight stable within 10% over the past year. Women with recurrence of breast cancer went off–study (n = 4:2 and 2 in the immediate and delayed treatment groups, respectively).

Intervention. The first 3 months of training, for all participants (regardless of group assignment), were supervised by an American College of Sports Medicine and/or National Strength and Conditioning Association certified fitness professional in small groups of four participants. These small training groups met twice weekly for 13 weeks, so that the trainers could teach the participants the safe and effective execution of all exercises in the protocol. If injuries or pain precluded performance of a particular exercise, modifications in the protocol were made at the discretion of the fitness professionals. After the first 13 weeks, the participants were expected to continue to train for an additional 13 weeks on their own. Participants were encouraged to train with other survivors, to foster the friendships formed during the first 13 weeks. Nine common weight-training exercises were performed using variable resistance machines and free weights (for muscles of the chest, back, shoulders, and arms, as well as the buttocks, hips, and thighs). The protocol for determining resistance differed for the upper versus the lower body to be sure that women with lymphedema (n = 14 with self-reported lymphedema at baseline) or at risk for lymphedema would not be placed at risk for onset or worsening of symptoms. *For the upper body*, participants started with no weight or 0.5 lb wrist weights for each exercise and progressed as symptoms allowed. If there was any worsening/onset of symptoms, the exercise associated with the symptoms was skipped, or a lighter weight was used, until the symptoms cleared up. *For the lower body*, a standard progressive weight-training approach was used in which participants lifted the most weight they could lift in each exercise 8 to 10 times in each set of repetitions. Participants built up to three sets per exercise over the first 2 to 3 weeks of exercise. For the first 3 months, the protocol for increasing weight on each lower body exercise was as follows: after two sessions during which a participant lifted the same weight 10 times during each completed set, the weight was increased by the smallest increment available for the exercise. For the remaining months of weight training, participants increased the weight after four sessions during which they lifted the same weight for 10, 10, and 12 repetitions for sets 1, 2, and 3, respectively. Once the women had learned all of the exercises, each exercise session lasted ~60 minutes.

During the first 6 months, participants kept exercise logs at the recreation center for monitoring by the fitness trainers. If a participant did not log at least one workout over a full week, a fitness trainer called to encourage her to complete a workout. During months 7 to 12, immediate group participants were

not required to record exercise sessions, although trainers continued tracking those who opted to continue to record sessions. No phone calls were made to immediate treatment group participants during months 7 to 12 to encourage workout completion.

Participants were instructed to allow normal seasonal variability in diet over the year of weight training but to not make any purposeful changes in diet that might result in gain or loss of body weight/fat. In addition, participants were asked not to make any changes in other elements of their exercise program (e.g., walking, bicycling, and swimming) while incorporating weight training.

Measurements. The Physical Activity Readiness Questionnaire was given during the telephone eligibility screening; it is a recommended preparticipation health screen to assess whether participation in exercise is safe for an individual (19). Each participant sent a form to her physician to request that the physician provide written permission for participation, as well as specifics of breast cancer diagnosis [date(s), stage, and grade of tumor] and treatment.

At months 6 and 12, all participants were asked whether they had experienced any injuries over the prior 6 months. The survey used was based on one developed and used for the HERITAGE family exercise study (20). If they responded yes, they were further asked about the type of injury, including heel spur, sprained ankle, shin splints, knee injury, hip injury, pulled/strained muscle, sprained wrist, back problems, or other. If a participant responded ''other,'' she was asked to describe her injury further. Participants were asked whether they believed the injury was the result of participation in the study, with response options including not sure, not at all, moderately, quite a bit, and entirely. No scale of severity of injuries or adverse events was used. However, no injury or adverse events occurred which would have been rated as ''severe'' or ''life threatening.'' Other questions on the injury survey included assessment of the effect of injury on exercise sessions (response options: no changes in exercise, substituted exercises, reduced sets or repetitions, continued same exercises with difficulty, and unable to do exercise), and an assessment of how the injury was on the day the survey was given: ''As of today, would you say that the injury is healing/resolved, improving, about the same, or getting worse.'' Arm circumferences and lymphedema symptoms were also assessed (21). We report only briefly about lymphedema-related results in this article. A detailed report of outcomes related to lymphedema is planned for a separate publication.

All other measurements were taken on all participants at three time points: baseline, 6, and 12 months later. Physiologic measures were taken at the University of Minnesota General Clinical Research Center by trained staff blinded to participant status. Participants were asked to refrain from physical activity for 48 hours before all measurements. Body weight and height measurements, blood draws, and dual energy X-ray absorptiometry (for body composition) were done between 6:30 and 11:00 a.m., after a 12-hour fast, and between 5 and 11 days after the start of menstrual flow for menstruating participants.

Anthropometric measurements included waist circumference, body weight, and height. Body weight was measured on a digital scale and stature was assessed using a mounted stadiometer, both calibrated weekly, with daily checks to ensure calibration was maintained (Scale-tronix 5005 stand-on digital scale; Scale-tronix, White Plains, NY). Waist circumference was taken at the level of the umbilicus. The same staff person, blinded to participant treatment status, took measurements on all participants at the three measurement time points using the same cloth measuring tape for all measurements. Body fat (percent and total), fat–free mass, and bone density were measured by dual energy X-ray absorptiometry in the total body scanning mode with a Lunar Prodigy dual-energy X-ray absorptiometry apparatus (software version 2.15; Lunar Radiation Corp., Madison, WI) at the General Clinical Research Center (22). Body fat percentage is expressed as percentage of non–bone tissue that was fat. The machine was calibrated monthly using phantoms of known composition; daily checks were done to ensure calibration was maintained.

The Baecke Questionnaire was given to assess participant physical activity outside of the weight-training protocol (23). This survey has been shown to have reliability and validity similar to or better than other self-report physical activity surveys (24). To assess usual food and nutrient intake the NIH-DHQ, a food frequency questionnaire (25) was given to all participants to complete at home and return at the strength testing session. In women, dietary outcomes from the gold standard of three 24-hour dietary recall instruments are more closely correlated with outcomes from the NIH-DHQ than from the Block or the Willett food frequency questionnaires (25). Several additional questions were given to assess current medication use (medication name, dose, and duration of use), as well as age, ethnicity, and education.

Fasting blood glucose and plasma insulin levels were measured at the Fairview University Diagnostic Laboratories (Minneapolis, MN). The glucose levels were assessed using colorometric reflectance spectrophotometry. Insulin levels were assessed by chemiluminescent immunoassay (Immulite, Diagnostic Products Corporation, Los Angeles, CA), and had an intra-assay coefficient of variability of 3.7% at 10 microunits/mL. Insulin resistance is the inverse of insulin sensitivity. The measure of insulin resistance used in this study was the homeostatic model assessment (HOMA) index. The HOMA index is calculated by multiplying fasting plasma insulin (mmol/L) by fasting glucose (mmol/L) and then dividing by 22.5 and correlates well ($r = -0.83$) with insulin sensitivity as measured by the gold standard euglycemic clamp measurement (26).

For assessment of IGF–axis variables, plasma samples were stored at −70°C and sent at study completion to Diagnostic Systems Laboratories reference laboratories (Webster, TX). Random samples were sent in duplicate to be tested for variation; the labs were blinded to which samples were sent in duplicate. ELISAs of IGF-I, IGF-II, IGFBP-1, IGFBP-2, and IGFBP-3 were done. Samples were run with two standard controls included in the kit for each analyte. The sensitivities for the assays for IGF-I, IGF-II, IGFBP-1, IGFBP-2, and IGFBP-3 were 0.03, 0.25, 0.04, 0.15, and 0.25 ng/mL, respectively. The intra-assay and interassay coefficients of variation for IGF-I were 6.5% at 167 ng/mL and 4.8% at 133 ng/mL, respectively; for IGF-II were 3.5% at 672 ng/mL and 5.2% at 939 ng/mL, respectively; for IGFBP-1 were 2.5% at 31 ng/mL and 6.8% at 30 ng/mL, respectively; for IGFBP-2 were 2.9% at 7.3 ng/mL and 3.1% at 5.7 ng/mL respectively; and for IGFBP-3 were 7.3% at 74 ng/mL and 8.2% at 66 ng/mL, respectively. All IGF–axis plasma assays were done in duplicate with the mean used for analysis; samples were batch processed to ensure the same reagent batch was used for all assays for a given participant. For all assays, technicians were blinded to treatment status.

Upper and lower body strength was assessed by one-repetition maximum tests (the maximum amount of weight that can be lifted once: 1 repetition maximum = 1 RM) for the bench press (upper body strength) and leg press (lower body strength) at the University of Minnesota Recreation Center. The intervention fitness trainers not blinded to participant treatment status did these tests. The trainers were given a script to follow while encouraging participants during strength testing so that their interactions would not differ across treatment and control participants. For the upper body, strength

assessments were symptom limited. One repetition maximum tests are the standard by which increases in muscular strength are evaluated (27) and have been found to be safe for most populations when properly supervised (27-29).

Statistical Analysis. Baseline characteristics of participants across the two treatment groups were compared using Student's *t* tests for continuous outcomes (with Scatterthwaite approximation if the variances were indicated as heterogeneous) and using χ^2 tests (or Fisher's two-sided exact tests) for categorical outcomes. Pearson correlation coefficients were calculated for outcome variables from baseline to 6 months.

Between–women comparisons of those randomized to immediate treatment versus delayed treatment for changes in body size, insulin, glucose, insulin resistance, and IGF–axis hormones across months 0 to 6 were made using Student's *t* tests after determining that adjustment for potential confounders did not alter the results. Confounders examined included postmenopausal status, baseline levels of sport and leisure physical activity, baseline level of energy intake (kilocalories), and 6-month changes in physical activity and energy intake.

Within–person comparisons were also made of changes in the delayed treatment group from months 7 to 12 (during treatment) versus months 0 to 6 (no treatment). These comparisons use the delayed treatment participants as their own controls. Again, Student's *t* tests were used after the same covariates were found to have no effect on the interpretation of the analytic results.

Additional analyses were done to assess whether the results would differ according to time since last session of cancer treatment, stage of cancer, time since first diagnosis, hormone blocker or aromatase inhibitor therapy at baseline (or changes in these therapies), changes in use of medications thought to affect body size, or types of adjuvant therapies undertaken (radiation and/or chemotherapy). As adjustment for covariates did not lead to any differences in interpretation, for simplicity only unadjusted analytic results are presented.

All tests are two sided. All statistical analyses were done using SAS version 8.2 (Cary, NC).

Results

Table 1 describes baseline characteristics of the 81 participants who completed baseline measures and did not have any recurrences over the course of the study. Overall, the two groups were similar at baseline. Except for one mixed-race woman in the immediate treatment group who reported both African American and Caucasian racial heritage, all of the women in the study were Caucasian. The majority of the participants had completed a college education and were postmenopausal, with a mean age of ~53, and an age range of 34 to 75. The majority of the participants had been diagnosed with stage I or II breast cancer, and the mean time since first diagnosis was between 18 and 24 months. Average time since last treatment was slightly over 1 year for both groups. The majority of the participants underwent radiation treatment, chemotherapy, and axillary dissection. Most of the women were taking Tamoxifen throughout the study. We were unable to collect data regarding diagnosis and treatment for two women (both in the immediate treatment group). Furthermore, we were unable to determine whether one delayed treatment group woman had undergone radiation therapy and one woman in the immediate treatment group declined to provide information on adjuvant pharmaceutical therapy at baseline. Therefore, the total sample sizes for breast cancer diagnosis and treatment variables varied from 38 to 39 for immediate treatment and from 40 to 41 for delayed treatment. Energy intake and leisure and sport physical activity scores indicate that the groups were similar with regard to diet and physical activity at baseline. No significant between group differences were noted in energy intake or physical activity scores changes from months 0 to 6 or from months 7 to 12 (data not shown).

Self-reported attendance at exercise sessions is provided in Table 2. The mean, median, minimum, and maximum are presented by treatment group allocation and study time period. From baseline to 6 months, only one of the women in the immediate treatment group attended <80% of the sessions. From months 7 to 12, 14 immediate treatment group women and four delayed treatment group women had attendance of

Table 1. Baseline characteristics of breast cancer survivors [mean (SD) or *n* (%)]

Variable	Immediate treatment	Delayed treatment	*P*
Age (y)	53.3 (8.7)	52.8 (7.6)	0.79
Ethnicity			
Caucasian	39 (98)	41 (100)	0.99
Mixed race	1 (2)		
Education			
Some college or vocational training	8 (20)	7 (17)	0.89
College degree	22 (55)	22 (54)	
Graduate or professional degree	10 (25)	12 (29)	
Postmenopausal	34 (85)	32 (78)	0.42
Breast cancer stage			
DCIS	7 (18)	5 (12)	0.63
Stage I	16 (43)	16 (39)	
Stage II	13 (34)	18 (44)	
Stage III	2 (5)	2 (5)	
Time since first diagnosis (y)	1.73 (min = 0.58, max = 3.59)	2.02 (min = 0.44, max = 11.42)	0.34*
Time since last treatment session (y)	1.21 (min = 0.28, max = 2.84)	1.09 (min = 0.25, max = 3.12)	0.45
Treatment types			
Radiation	25 (66)	26 (65)	0.91
Chemotherapy	25 (66)	30 (73)	0.48
Axillary dissection	33 (87)	39 (95)	0.25 †
Hormone blocker treatment			
Tamoxifen	30 (77)	27 (66)	0.27
Anastrazole	3 (8)	5 (12)	0.72 †
Other	0 (0)	1 (2)	
Energy intake (kcal)	1,577 (721)	1,495 (568)	0.58
Leisure physical activity score (units)	2.53 (0.48	2.58 (0.52)	0.70
Sport physical activity score (units)	3.23 (0.69)	3.18 (0.63)	0.75

*Scatterthwaite test.
† Fisher's two-sided exact test.

Table 2. Participant attendance

	Immediate treatment group* (%)				Delayed treatment group (%)			
	Mean	Median	Minimum	Maximum	Mean	Median	Minimum	Maximum
0-6 mos	92	96	40	112	NA	NA	NA	NA
6-12 mos	66	77	0	108	88	90	50	112
All 12 mos	80	87	44	104	NA	NA	NA	NA

Abbreviation: NA, not applicable.
*Immediate treatment group participants were only *required* to record attendance during the first 6 mos of training. Therefore, data for mos 6 to 12 and all 12 mos may be underestimates, as some women chose to exercise but not record their sessions consistently.

<70%. Values for months 7 to 12 and the full 12 months may be underestimates for the immediate treatment group participants, given that these women were not required to record exercise sessions during their second 6 months of training. Additional evidence of excellent adherence is provided by examining changes in strength over time. For example, the % changes in bench press 1-RM tests over the first 6 months were 63% in immediate versus 12% in delayed treatment groups ($P < 0.001$). The delayed treatment group increased bench press strength 1-RM by 36% from 7 to 12 months ($P < 0.001$ for t test compared with change from baseline to 6 months). The leg press 1-RM increases were 38% for immediate and 9% for delayed treatment groups over the first 6 months and 39% for the delayed treatment group from months 7 to 12 ($P < 0.001$ for t tests of both parallel group and within−person comparisons).

Table 3 shows the body size values (mean ± SD), by treatment allocation, at each measurement time point, as well as the changes over the first 6 months (the period of the randomized controlled trial) and the changes over months 7 to 12 (the period during which the immediate treatment group continued training and the delayed treatment group began training). This table also includes P values for the comparison of changes over the first 6 months across treatment allocation (the randomized controlled trial effect) and the P values for comparison of changes in the delayed treatment group over 12 months, comparing change during months 7 to 12 (weight training) versus change during months 0 to 6 (no exercise). The results indicate that there were significant effects of weight training on lean mass and body fat % but not for body weight, BMI, body fat, or waist circumference. The within-person control comparison for body fat % did approach significance (−1.10% versus 0.22%, $P = 0.08$). No differences were noted when the changes over the first 6 months of weight training were compared between the immediate and delayed treatment groups. Adjustment for changes in energy intake and physical activity outside of weight training did not alter the findings presented in Table 3 (results not shown). Pearson's correlation coefficients for baseline and 6-month values for body size variables ranged from 0.94 for waist circumference to 0.99 for body weight.

Table 4 is organized in a manner similar to Table 3 and presents the changes in insulin, glucose, and a measure of insulin resistance (HOMA), as well as IGF-I, and -II, and IGFBP-1, IGFBP-2, and IGFBP-3. Insulin and the HOMA index were both severely skewed, but reanalysis with log-transformed values of these outcomes did not alter the interpretation of the comparisons and thus are not presented. The intervention significantly decreased IGF-II levels in both groups after 6 months of weight training when compared with a concurrent comparison group or using within person controls ($P = 0.02$ for both comparisons). Levels of IGFBP-3 were significantly decreased in the delayed treatment group after 6 months of training compared with the change experienced during the 6 months not training ($P = 0.03$). No other intervention effects were

Table 3. Body size changes over 6 or 12 mos of weight training

Variable name	Baseline		6 mos		12 mos		Δ0-6 mos	P for 0-6 mo differences*	Δ6-12 mos	P for within-person control tests †
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	Mean ± SD		Mean ± SD	
Body weight (kg)										
Immediate treatment‡	40	69.21 ± 2.22	39	69.54 ± 2.22	33	69.15 ± 2.23	0.32 ± 0.43	0.84	−0.38 ± 0.46	0.76
Delayed treatment§	41	68.96 ± 2.20	40	69.16 ± 2.20	36	69.59 ± 2.20	0.20 ± 0.42		0.43 ± 0.44	
BMI (kg/m^2)										
Immediate treatment‡	40	25.94 ± 0.73	39	25.99 ± 0.74	33	25.81 ± 0.74	0.06 ± 0.17	0.95	−0.18 ± 0.18	0.77
Delayed treatment§	41	25.76 ± 0.73	40	25.83 ± 0.73	36	25.98 ± 0.73	0.07 ± 0.16		0.15 ± 0.17	
Body fat (kg)										
Immediate treatment‡	40	28.81 ± 1.72	39	28.29 ± 1.72	33	27.34 ± 1.73	−0.52 ± 0.43	0.23	−0.95 ± 0.46	0.08
Delayed treatment§	41	28.75 ± 1.70	40	28.97 ± 1.70	36	27.87 ± 1.70	0.22 ± 0.43		−1.10 ± 0.45	
Lean mass (kg)										
Immediate treatment‡	40	37.90 ± 0.77	39	38.78 ± 0.77	33	39.29 ± 0.78	0.88 ± 0.23	0.008	0.50 ± 0.24	<0.0001
Delayed treatment§	41	37.64 ± 0.76	40	37.66 ± 0.77	36	39.11 ± 0.77	0.02 ± 0.23		1.45 ± 0.24	
Body fat %										
Immediate treatment‡	40	42.05 ± 1.31	39	40.91 ± 1.31	33	39.82 ± 1.32	−1.15 ± 0.45	0.03	−1.08 ± 0.48	0.003
Delayed treatment§	41	42.05 ± 1.29	40	42.29 ± 1.30	36	40.21 ± 1.30	0.23 ± 0.44		−2.07 ± 0.46	
Waist circumference (cm)										
Immediate treatment‡	40	94.44 ± 2.01	39	94.59 ± 2.02	33	92.53 ± 2.05	0.14 ± 1.05	0.39	−2.05 ± 1.12	0.22
Delayed treatment§	41	93.04 ± 1.98	40	94.45 ± 1.99	36	93.61 ± 2.01	1.41 ± 1.04		−0.84 ± 1.08	

*P from test for comparing the changes in the immediate treatment group to the changes in the delayed treatment group over the first 6 mos of the study (randomized controlled trial).
† P from test for comparing the delayed treatment group changes from mos 7 to 12 to the delayed treatment group changes from mos 0 to 6 (within person control).
‡ The immediate treatment group trained from 0 to 12 mos continuously.
§ The delayed treatment group started training after the 6-mo measures were complete and through 12 mos.

Table 4. Changes in insulin, glucose, insulin resistance, and IGF axis variables over 6 or 12 mos of weight training

Variable name	Baseline		6 mos		12 mos		Δ0-6 mos (mean ± SD)	*P* for 0-6 mo differences*	Δ6-12 mos (mean ± SD)	*P* for within-person control tests†
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD				
Glucose (mg/d)										
Immediate treatment‡	39	92.19 ± 1.85	37	88.49 ± 1.88	33	94.40 ± 1.95	−3.70 ± 1.71	0.90	−4.09 ± 1.80	0.17
Delayed treatment§	41	91.73 ± 1.82	39	88.35 ± 1.85	35	89.02 ± 1.90	−3.38 ± 1.66		0.67 ± 1.73	
Insulin (microunits/mL)										
Immediate treatment‡	38	7.66 ± 0.69	37	8.21 ± 0.69	33	7.01 ± 0.71	0.55 ± 0.51	0.79	−1.20 ± 0.53	0.46
Delayed treatment§	41	7.59 ± 0.67	40	7.94 ± 0.67	35	7.65 ± 0.69	0.35 ± 0.49		−0.29 ± 0.51	
HOMA (units)‖										
Immediate treatment‡	38	1.74 ± 0.19	36	1.79 ± 0.19	33	1.46 ± 0.20	0.05 ± 0.15	1.00	−0.32 ± 0.15	0.78
Delayed treatment§	41	1.76 ± 0.18	39	1.80 ± 0.19	35	1.78 ± 0.19	0.05 ± 0.14		−0.02 ± 0.15	
IGF-I (ng/mL)										
Immediate treatment‡	38	172.93 ± 11.58	39	181.22 ± 11.55	32	176.63 ± 11.82	8.29 ± 6.26	0.16	−4.60 ± 6.62	0.64
Delayed treatment§	40	194.26 ± 11.40	40	190.30 ± 11.41	35	191.28 ± 11.57	−3.97 ± 6.10		0.98 ± 6.36	
IGF-II (ng/mL)										
Immediate treatment‡	38	898.01 ± 34.92	39	871.77 ± 34.85	32	870.11 ± 35.48	−26.23 ± 16.73	0.02	−1.16 ± 17.69	0.02
Delayed treatment§	40	891.26 ± 34.40	40	919.54 ± 34.42	35	879.32 ± 34.81	28.28 ± 16.31		−40.22 ± 17.00	
IGFBP-1 (ng/mL)										
Immediate treatment‡	38	36.86 ± 2.88	39	34.73 ± 2.86	32	35.52 ± 3.00	−2.14 ± 2.32	0.36	0.79 ± 2.45	0.47
Delayed treatment§	40	36.94 ± 2.82	40	37.75 ± 2.83	35	35.67 ± 2.92	0.81 ± 2.26		−2.07 ± 2.36	
IGFBP-2 (ng/mL)										
Immediate treatment‡	38	421.72 ± 29.51	39	449.63 ± 29.42	32	451.09 ± 30.17	27.91 ± 16.83	0.30	1.46 ± 17.80	0.89
Delayed treatment§	40	472.86 ± 29.04	40	476.45 ± 29.06	35	484.08 ± 29.53	3.58 ± 16.42		7.63 ± 17.11	
IGFBP-3 (ng/mL)										
Immediate treatment‡	38	4,339.66 ± 133.17	39	4,356.20 ± 132.66	32	4,380.96 ± 136.94	16.54 ± 85.89	0.32	24.76 ± 90.79	0.03
Delayed treatment§	40	4,519.72 ± 130.91	40	4,655.05 ± 131.02	35	4,470.66 ± 133.72	135.33 ± 83.79		−184.4 ± 87.3	

*P from test for comparing the changes in the immediate treatment group to the changes in the delayed treatment group over the first 6 mos of the study (randomized controlled trial).
†P from test for comparing the delayed treatment group changes from mos 7 to 12 to the delayed treatment group changes from mos 0 to 6 (within-person control).
‡The immediate treatment group trained from 0 to 12 mos continuously.
§The delayed treatment group started training after the 6-mo measures were complete and through 12 mos.
‖Put HOMA units here (can not remember them right now).

noted. Pearson's correlation coefficients for baseline and 6-month values of glucose, log of insulin, log of HOMA, IGF-I, IGF-II, IGFBP-1, IGFBP-2, and IGFBP-3 were 0.70, 0.66, 0.68, 0.85, 0.88, 0.74, 0.82, and 0.85, respectively.

Table 5 highlights injuries incurred by participants during the time they were participating in the study by treatment allocation and time period. None of the four immediate treatment women who reported back problems during the first 6 months reported being unable to exercise as a result of a study-related injury. One immediate treatment group participant reported at 12 months that she was unable to exercise due to an injury related to the study (wrist injury) and that the injury was getting worse. The rest of these women reported continuing exercise sessions, either substituting exercises or reduced sets to deal with a minor injury. There was no difference in self-report of clinical diagnoses of lymphedema across treatment and delayed treatment groups over the first 6 months (results not shown). There was also no difference in self-report of clinical diagnoses of lymphedema when comparing the delayed treatment group from months 6 to 12 versus baseline to 6 months (results not shown). There was no effect of the intervention on arm circumference changes either,

Table 5. Injuries and illnesses by treatment allocation and timing

Baseline to 6 mos		7 to 12 mos	
Types and no. occurrences for injuries not related to study participation	Types and no. occurrences of injuries moderately, quite a bit or entirely related to study participation	Types and no. occurrences for injuries not related to study participation	Types and no. occurrences of injuries moderately, quite a bit or entirely related to study participation
Immediate treatment			
Shin splints (*n* = 1) Wrist injury (*n* = 1) Other: muscle strain from mowing lawn (*n* = 1)	Back injury (*n* = 4)	Back injury (*n* = 3) Heel spur (*n* = 1) Other: rotator cuff injury (*n* = 1) Other: slipped and fell, bruised (*n* = 1) Other: elbow tendonitis (*n* = 1)	Back injury (*n* = 2) Wrist injury (*n* = 1) Other: leg pain (*n* = 1)
Delayed treatment			
Back injury (*n* = 1) Ankle injury (*n* = 2) Wrist injury (*n* = 3) Other: joint pain (*n* = 1)	Other: shoulder tendonitis (*n* = 1)	Back injury (*n* = 4) Heel spurs (*n* = 1) Ankle injury (*n* = 1) Wrist injury (*n* = 2) Other: Large bruise (*n* = 1) Other: knee pain and plantar fascitis (*n* = 1) Other: leg pain/numbness (*n* = 1)	Back injury (*n* = 2) Heel spurs (*n* = 1) Ankle injury (*n* = 3) Other: rotator cuff injury (*n* = 1)

in the between- or within-group comparisons (results not shown). The most severe injuries altered activities of daily living for a period of several weeks, with no known long-term negative effects.

Discussion

The Weight Training for Breast Cancer Survivors (WTBS) study is the first study to evaluate the effects of weight training on body size variables and biomarkers for breast cancer among breast cancer survivors. The intervention led to significant increases in lean muscle mass, as well as reduced body fat percentage and IGF-II. A significant decrease in IGFBP-3 was noted in the delayed treatment group when compared with the IGFBP-3 change in the same group over 6 months not exercising. There were no effects on body weight, BMI, body fat, waist circumference, insulin, glucose, insulin resistance, IGF-I, or any of the IGF-binding proteins.

It is unlikely that the changes noted in body composition are clinically relevant in the short term. The context in which they may become clinically relevant may be longer term. We have shown that strength training is behaviorally feasible for breast cancer survivors. If this behavior change can be maintained over time, the differences in body composition between survivors who continue weight training over multiple years and survivors who remain sedentary may become clinically relevant. To place this in context, it may be useful to note that differences of 5.9 kg (presumably largely differences in fat weight) have been shown to be meaningful with regard to breast cancer recurrence (13). If the women in our study maintain strength training over time, it is possible they will prevent the increase in body fat that tends to occur over time in midlife. Because weight gain tends to be between 1 and 2 kg per year in the general population (30), this could become clinically meaningful in 5 years. We saw no changes in insulin, glucose, or IGF–axis proteins that we think are likely to become clinically meaningful.

To our knowledge, there is only one prior published exercise intervention study to examine similar outcomes in recent breast cancer survivors. The REHAB study (31) assessed the effects of a 15-week aerobic exercise intervention on postmenopausal breast cancer survivors. Comparison of exercise dose between REHAB and WTBS is made difficult by the differing modes of activity. The REHAB study participants were similar to participants in WTBS as to time since treatment, but REHAB participants were older and had higher BMI levels at baseline. Similarities in the results between the two studies include no changes in fasting glucose, insulin, or insulin resistance, as well as no changes in IGFBP-1. In contrast to WTBS, the REHAB trial showed significant decreases in IGF-I and the molar ratio of IGF-I to IGFBP-3, as well as an increase in IGFBP-3. Only half of the participants in the REHAB trial were taking tamoxifen compared with 77% of intervention participants in WTBS. This might explain the significant reduction of IGF-I in REHAB but not in WTBS, because tamoxifen has been shown to reduce IGF-I levels by 16% (32) at the usual dose of 20 mg/d. It is possible that exercise cannot further reduce IGF-I below the reductions obtained by tamoxifen. WTBS showed a significant decrease in IGF-II, whereas the REHAB trial showed similar decreases that were only marginally significant ($P = 0.10$). Furthermore, WTBS showed a decrease in body fat % and an increase in lean mass, whereas the REHAB trial showed no statistically significant changes in body composition. Explanations for the differing findings with regard to body composition may include the differing modes of exercise and the less sensitive measure of body composition used in the REHAB trial (skinfolds) than the whole body dual-energy X-ray absorptiometry scan used in WTBS.

The delayed treatment group experienced the same body size changes over 6 months of training that the immediate treatment group experienced after 12 months of training. This finding was not observed to be the result of time since treatment. We speculate that the women in the immediate treatment group were more tenuous when they started training, as they had no role models who could show them what they were capable of doing. By comparison, by the time the delayed treatment group started training, there were 40 breast cancer survivors using the University Recreation Center who were lifting weights and serving as role models.

It can also be noted that all of the body size effects were more pronounced at 12 months than at 6 months in the immediate treatment group, which is promising regarding sustainability and further improvements over time. Lack of a concurrent comparison group limits the ability to draw strong conclusions from these 12-month ''maintenance'' results in the immediate treatment group. Additional longer exercise interventions are needed to ascertain the long-term effects of weight training on breast cancer survivors.

The results from the WTBS injury survey indicate that twice-weekly weight training is well tolerated by recent breast cancer survivors. Injury rates in the general population have been observed to be 2.4% per month of weight training (33). Assuming injury rates to be constant over time, we would expect an injury rate of 14.4% per 6 months or 28.8% over 1 year. The immediate treatment group experienced an injury rate of 10.5% over the first 6 months and a total of 22.5% over the full year. The delayed treatment group experienced an injury rate of 20% over their first 6 months of training. The reported injuries were minor; only one woman was injured severely enough to stop exercising. Although the rate of injury in the delayed treatment group over months 7 to 12 is higher than observed in the general population, the relatively minor injuries incurred suggest that weight lifting is as safe for recent breast cancer survivors as for the general population. The most commonly reported problems were for back injury. Future weight training interventions should add additional intervention components to strengthen the core musculature (abdominal, low back, and pelvic floor).

Strengths of this study include that the women were screened before study entry to be less than moderately physically active, the randomized controlled design with an intention to treat analysis, and measurement of obvious confounders (e.g., exercise other than weight training and dietary changes). Furthermore, this intervention was longer than most exercise interventions that have been conducted in breast cancer survivors and assessed the effect of a novel exercise mode: weight training. Finally, the standardized measurement of injuries at each measurement time point provides unique data on the safety of weight training for breast cancer survivors. Weaknesses of the study include the lack of a concurrent comparison group out to 12 months for the immediate treatment group. The heterogeneity of the participant sample with regard to age, stage of cancer, treatment modalities, and diagnosis of lymphedema at baseline can be seen as a weakness or as a strength, depending on whether the goal is to generalize to all breast cancer survivors or to prescribe the intervention for a very specific subset of survivors. Finally, although we did systematically assess injuries and adverse events, the scale for doing so was drawn from a previous exercise intervention study and not an established toxicity grading scale. To our knowledge, no such scale currently exists specifically for exercise interventions among cancer survivors. Development of a systematic adverse events and injuries scale for exercise interventions in cancer survivors would assist in establishing the safety of exercise training in this population.

The results reported herein support several types of additional trials. A repeat of the same study described herein would be of value in two specific subsets of breast cancer survivors: diabetics and those who have completed hormonal therapies. We hypothesize that one explanation for the lack of

changes in the IGF axis in the current study could be that the hormonal therapies taken by the participants may have reduced IGF-I as much as it could be reduced. A repeat of this intervention in women who have completed hormonal therapy would enable this hypothesis to be tested. Finally, the effect of the same intervention on breast cancer survivors with diabetes or impaired glucose tolerance would be of interest to know whether the reason for the lack of changes in insulin, glucose, and the IGF–axis was because the women were at ''normal'' levels for these values at study entry. When there is no physiologic advantage to altering/lowering values of some purported risk factor, exercise should not be expected to alter the variable. More generally, a 5-year follow-up is needed of women just diagnosed with breast cancer to assess whether regular exercise would alter a 5-year survival. These studies could be observational and/or interventional.

In conclusion, twice-weekly weight training is a safe, behaviorally feasible exercise program for recent breast cancer survivors that will likely result in increased muscle mass, as well as decreased body fat percentage and IGF-II. The implications of these results on cancer recurrence or survival may become more evident with additional large, long-term randomized controlled exercise intervention trials in breast cancer survivors. However, the prospects are excellent for the safety of weight training for rehabilitation and health promotion benefits among breast cancer survivors.

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