

Weight Lifting in Women with Breast-Cancer-Related Lymphedema

Kathryn H. Schmitz, Ph.D., M.P.H., Rehana L. Ahmed, M.D., Ph.D.,
 Andrea Troxel, Sc.D., Andrea Cheville, M.D., Rebecca Smith, M.D.,
 Lorita Lewis-Grant, M.P.H., M.S.W., Cathy J. Bryan, M.Ed.,
 Catherine T. Williams-Smith, B.S., and Quincy P. Greene

ABSTRACT

BACKGROUND

From the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine and Abramson Cancer Center, Philadelphia (K.H.S., A.T., R.S., L.L.-G., C.J.B., C.T.W.-S., Q.P.G.); the Department of Dermatology, University of Minnesota Medical School, Minneapolis (R.L.A.); and the Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN (A.C.). Address reprint requests to Dr. Schmitz at the Department of Biostatistics and Epidemiology, University of Pennsylvania, 423 Guardian Dr., 903 Blockley Hall, Philadelphia, PA 19104-6021, or at schmitz@mail.med.upenn.edu.

Weight lifting has generally been proscribed for women with breast-cancer-related lymphedema, preventing them from obtaining the well-established health benefits of weight lifting, including increases in bone density.

METHODS

We performed a randomized, controlled trial of twice-weekly progressive weight lifting involving 141 breast-cancer survivors with stable lymphedema of the arm. The primary outcome was the change in arm and hand swelling at 1 year, as measured through displaced water volume of the affected and unaffected limbs. Secondary outcomes included the incidence of exacerbations of lymphedema, number and severity of lymphedema symptoms, and muscle strength. Participants were required to wear a well-fitted compression garment while weight lifting.

RESULTS

The proportion of women who had an increase of 5% or more in limb swelling was similar in the weight-lifting group (11%) and the control group (12%) (cumulative incidence ratio, 1.00; 95% confidence interval, 0.88 to 1.13). As compared with the control group, the weight-lifting group had greater improvements in self-reported severity of lymphedema symptoms ($P=0.03$) and upper- and lower-body strength ($P<0.001$ for both comparisons) and a lower incidence of lymphedema exacerbations as assessed by a certified lymphedema specialist (14% vs. 29%, $P=0.04$). There were no serious adverse events related to the intervention.

CONCLUSIONS

In breast-cancer survivors with lymphedema, slowly progressive weight lifting had no significant effect on limb swelling and resulted in a decreased incidence of exacerbations of lymphedema, reduced symptoms, and increased strength. (ClinicalTrials.gov number, NCT00194363.)

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THERE ARE MORE THAN 2.4 MILLION SURVIVORS of breast cancer in the United States.¹ Approximately 184,000 women are diagnosed with breast cancer each year in the United States, and 90% of these women will live at least 5 years.² Improvements in immediate treatment outcomes have led to an increased focus on morbidity among survivors. Lymphedema ranks high among the serious concerns of survivors, as it is chronic, progressive, and incurable.³ Lymphedema causes limb swelling and discomfort, considerably impairing arm function.⁴ The incidence of lymphedema after breast-cancer surgery varies across studies from 6 to 70%, depending on the criteria used for diagnosis and the follow-up interval.⁵⁻⁷ Sentinel-lymph-node biopsy is associated with a lower risk of lymphedema than axillary dissection,⁸ but one study reported a 17% incidence after sentinel-lymph-node biopsy alone.⁹

Breast-cancer survivors with lymphedema may limit the use of their affected arm out of fear and on the basis of guidance from commonly accessed cancer-information Web sites,^{10,11} which suggest that risk of lymphedema is decreased by avoiding lifting children, heavy bags, or other objects with the affected arm. Although this advice is intended to prevent harm, adherence to these precautions may limit physical recovery after breast-cancer surgery, alter activities, and adversely affect employment. Conversely, a program of controlled exercise through weight lifting may increase the physical-work capacity of the affected arm, thereby protecting it from injury sustained during common daily activities. Weight lifting offers additional benefits particularly relevant to breast-cancer survivors, including control of body fat^{12,13} and improved functional outcomes and bone health.¹⁴⁻¹⁶ We performed a 1-year randomized, controlled trial involving breast-cancer survivors with lymphedema to assess the effects of controlled weight lifting.

METHODS

PATIENTS

A total of 141 women with a history of breast cancer and current lymphedema were recruited from October 2005 through March 2007; follow-up was completed by August 2008. Recruitment methods included letters sent by state cancer registries, advertisements and interviews, and flyers.

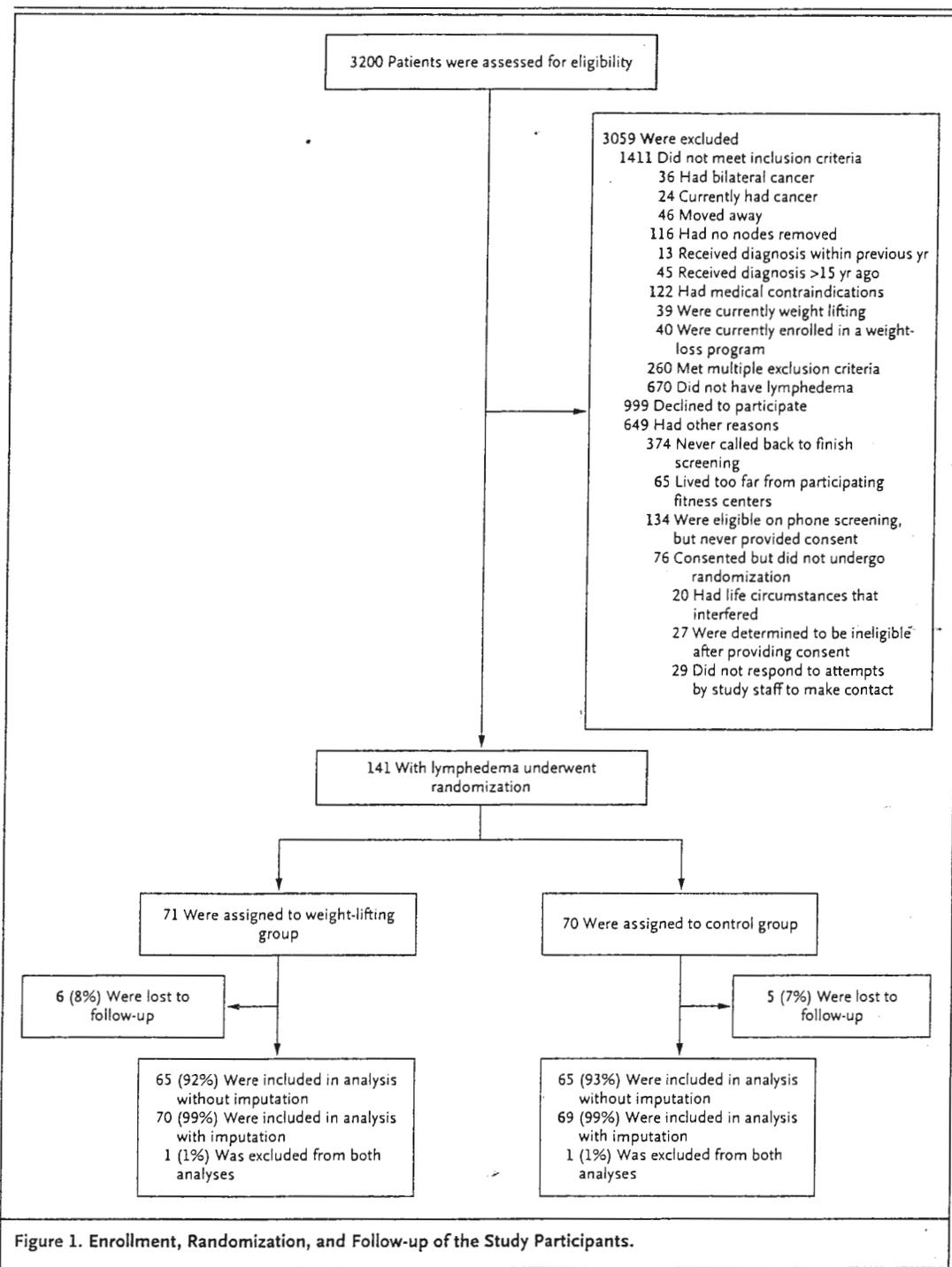
Eligible women had a history of unilateral non-metastatic breast cancer 1 to 15 years before study entry and a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 50 or less, were not actively trying to lose weight, and had no current evidence of cancer, no medical conditions that would limit exercise, no history of weight lifting during the previous year, at least one lymph node removed, and a clinical diagnosis of stable breast-cancer-related lymphedema. Lymphedema was defined as a difference in the volume or circumference between the affected and unaffected limb of 10% or more or, according to Common Toxicity Criteria,¹⁷ arm swelling, obscuration of the anatomical architecture of the arm, or pitting edema. If a woman reported having lymphedema but it was not evident at study entry, she was required to provide written documentation of a previous clinical diagnosis of lymphedema and treatment from a certified lymphedema therapist.¹⁸ Stable lymphedema was defined as the absence in the past 3 months of therapist-delivered treatment, more than one arm infection requiring antibiotics, change in ability to perform activities of daily living, and verified changes in arm swelling of more than 10%.

Figure 1 shows the enrollment, randomization, and follow-up of the study participants. Women were assigned to either of two equal-size groups through a computerized process called minimization,^{19,20} in a manner that was unpredictable and was concealed from the study staff who determined eligibility. This approach balanced important potential confounders at baseline: age (<54 years vs. ≥54 years), difference in the volume between the affected and unaffected limbs (<10% vs. 10 to 20% vs. >20%), number of lymph nodes removed (<6 vs. ≥6), obesity (BMI <30 vs. ≥30), months since diagnosis (<60 vs. ≥60), and history of radiation treatment (yes vs. no).

The Institutional Review Board of the University of Pennsylvania approved the protocol. Before participating, women provided written informed consent and written clearance from a physician.

MEASUREMENTS

Measurements were obtained for all participants at baseline and at 12 months by trained staff who were unaware of the study-group assignments, using standardized methods. Limb volume was measured by submerging the arm and hand in



water and measuring the displaced water volume.^{21,22} All participants were also evaluated by a certified lymphedema therapist¹⁸ using the Common Toxicity Criteria, which assess the tone, texture, and anatomical architecture of the arm tissue, in addition to swelling.¹⁷ Participants com-

pleted a validated survey assessing the presence and severity of 14 lymphedema-related limb symptoms (including swelling, leathery skin texture, heaviness, pain, pitting, and difficulty writing).²³ Lymphedema exacerbations were ascertained by certified lymphedema specialists¹⁸ who were

unaware of the study-group assignments, using a standardized evaluation. The participant was deemed to have an exacerbation if there was an increase in the volume of the affected limb of 5% or more, accompanied by an increase of 5% or more in the difference in the volume or circumference between the affected and unaffected limbs and by indications of sustained tissue changes such as fibrosis (sponginess, pitting, or hard, nonpitting fibrosis), altered skin color, or alteration of activities of daily living over the previous week because of symptoms (e.g., heaviness, inability to grip, tiredness, or achiness). Participants were evaluated for possible exacerbation if they reported a change in symptoms lasting 1 week or longer or if interim measurements at 3 or 6 months, by staff who were unaware of the study-group assignments, indicated an increase in the volume of the affected limb and an interlimb difference of 5% or more.

For each participant, the maximum amount of weight that could be lifted once was assessed for the bench press and leg press at baseline and 12 months; these tests are considered safe for most populations if properly supervised.²⁴⁻²⁶ The initial weight attempted for this test was based on the participant's rating of the difficulty of a warm-up set of four to six repetitions (40 lb [18.1 kg] for leg press, 5 lb [2.3 kg] for bench press), performed after stretching and familiarization with the equipment. Resistance was added until the participant rated the difficulty as maximal and refused to try to lift more, was clearly unable to lift more with proper biomechanics, or reported a symptom that required stopping. Trained study staff encouraged participants according to a standardized script. Compliance with the weight-lifting intervention was evaluated by means of attendance logs completed by fitness trainers.

Demographic characteristics were self-reported by patients at baseline. The cancer stage was obtained for each patient from state registries. Treatment history was self-reported, except for the number of lymph nodes removed, which was derived from pathology reports. Measurements assessed at baseline and at 12 months included weight and height, whole-body dual-energy x-ray absorptiometry (Hologic Discovery), adherence to common lymphedema self-care activities (e.g., compression, massage, bandaging), physical activity outside of weight lifting (according to the

International Physical Activity Questionnaire)²⁷; and diet (according to the Diet History Questionnaire).^{28,29}

WEIGHT-LIFTING PROGRAM

Participants assigned to the weight-lifting group received a 1-year membership at a community fitness center (e.g., a YMCA) near their home. For the first 13 weeks, women were instructed, in small groups in a 90-minute session, twice weekly. Certified fitness professionals employed by the fitness centers led these sessions, which included stretching, cardiovascular warm-up, abdominal and back exercises, and weight-lifting exercises. Upper-body exercises included seated row, chest press, lateral or front raises, bicep curls, and tricep pushdowns. Lower-body exercises included leg press, back extension, leg extension, and leg curl. Weight-lifting exercises were introduced with little-to-no resistance. One to three new exercises were taught per session.

During the first 5 weeks, participants increased their number of sets of each exercise per session from two to three, with 10 repetitions per set. If no changes in symptoms were noted for a particular exercise after two sessions at a given weight, the resistance was increased by the smallest possible increment. If fatigue prevented the completion of a third set of 10 repetitions of a given exercise with proper biomechanical form, resistance for that exercise would remain the same at the next session. After two sessions at which three sets of 10 repetitions could be performed with proper form at a given level of resistance, without changes in arm and hand symptoms, the trainer guided the participant to increase the resistance by the smallest possible increment at the next session. No upper limit was placed on the weight to which women could progress in any exercise. During lymphedema exacerbations, women continued all exercises except the upper-body exercises, which were resumed only after approval of their lymphedema therapist, with resistance reset to the lowest possible level and then increased again as described above.

After the first 13 weeks, participants continued twice-weekly unsupervised exercise for 39 additional weeks. Throughout the study, fitness trainers telephoned women who missed more than one session per week. Participants in the control group were asked not to change their exercise level during study participation and were

offered a 1-year fitness-center membership, with 13 weeks of supervised instruction, after study completion. The exercise protocol and the sequence in which the exercises were taught are available on request.

SAFETY

Trainers who worked with participants underwent 3 days of training, including an overview of lymphedema prevention, symptoms, and treatment³⁰⁻³² and the exercise protocol. At baseline and 6 months, participants in both groups were given a custom-fitted compression garment (Jobst, BSN Medical). Participants in the weight-lifting group were required to wear these garments during weight lifting. Trainers asked the participants about changes in symptoms weekly, and measured the circumference and water volume of both limbs monthly, to ensure that any changes were detected promptly. Finally, participants in both groups were required to attend a 1-hour educational lecture that reviewed the National Lymphedema Network guidelines for risk reduction, treatment, and exercise.³⁰⁻³² The 2005 guidelines included the statement that strength training is the type of exercise that "poses the greatest risk to individuals with lymphedema" and that modifications to strength training (e.g., adequate rest intervals or appropriate and sufficient compression of the affected limb) may be indicated.

STUDY OUTCOMES

The prespecified primary comparison between the weight-lifting group and the control group was the proportion of participants with an absolute increase of 5 percentage points or more in the interlimb volume discrepancy (the interlimb difference over time). Prespecified secondary outcomes included lymphedema exacerbation and symptoms, as well as strength and anthropometric measures.

STATISTICAL ANALYSIS

Descriptive statistics reported for baseline variables include rates for binary variables and means or medians and standard deviations for continuous variables. Data for two participants (one with a second primary cancer and one with recurrent cancer) were excluded. Data on the interlimb volume difference for nine women who were lost to follow-up were imputed with the use of predicted values from a multiple linear regression analysis

that included baseline predictors. Continuous outcomes were compared between the two study groups by means of the Wilcoxon rank-sum test. For the analysis of data on exacerbations, simple imputation-based sensitivity analyses were conducted, in which the nine participants lost to follow-up were assumed to have had an exacerbation and then not to have had an exacerbation. Binary outcomes were compared between the two study groups using Fisher's exact test, with a two-sided significance level of 0.05.

Sample-size calculations were based on the aim of demonstrating equivalence between the weight-lifting group and the control group with respect to the primary outcome of changes in arm and hand swelling, as measured by displaced water volume. The statistical power of the study was set at 80%, with a significance level of 0.05, allowing for loss to follow-up of 20% of participants. Given these parameters and a null hypothesis of nonequivalence (a between-group difference of >20% in the proportion of women who had an increase of 5 percentage points in the interlimb volume discrepancy), we sought to recruit 144 women with lymphedema to provide adequate power against an alternative equivalence hypothesis (a between-group difference of <5% in the proportion of participants who had an absolute increase of at least 5 percentage points in the interlimb volume discrepancy).

RESULTS

Table 1 summarizes baseline characteristics of all participants, including the two (1%) who were excluded from the analyses because of a second primary or recurrent cancer and the nine (6%) who were lost to follow-up. All participants had a clinical diagnosis of lymphedema; 12 had lymphedema classified as grade 0 at baseline but were included because, once diagnosed, lymphedema is considered to be manageable but not curable. The median rates of exercise-session attendance were 96%, 88%, 81%, and 75% in the first, second, third, and final quarters of the year-long study, respectively. There were no significant differences between the two groups in the baseline values of measures of strength, anthropometric data, diet, and physical activity (Table 2).

At 12 months, the weight-lifting participants had increased their strength, as measured with the bench press and leg press, more than controls

Table 1. Baseline Characteristics of the 141 Study Participants with Lymphedema, According to Study Group.*

Characteristic	Weight Lifting (N=71)	Control (N=70)	P Value
Age — yr	56±9	58±10	0.56
Education — no. (%)			0.80
High school or less	13 (18)	16 (23)	
Some college	26 (37)	24 (34)	
College degree or more	32 (45)	30 (43)	
Self-reported race — no. (%)			0.87
White	40 (56)	42 (60)	
Black	28 (39)	26 (37)	
Other	3 (4)	2 (3)	
Occupation — no. (%)			0.15
Professional	29 (41)	23 (33)	
Clerical or service	10 (14)	11 (16)	
Homemaker, student, or unemployed	8 (11)	4 (6)	
Other or unknown	9 (13)	4 (6)	
Retired	15 (21)	28 (40)	
Months since cancer diagnosis	79±45	88±45	0.23
Cancer stage — no. (%)			0.19
1	33 (46)	24 (34)	
2	1 (1)	0	
3	22 (31)	22 (31)	
Data not available	15 (21)	24 (34)	
No. of nodes removed	15±8	16±8	0.59
Chemotherapy — %	83	80	0.67
Radiation — %	83	76	0.30
Current receipt of drugs — %			
Tamoxifen	20	4	0.008
Aromatase inhibitor	0	1	0.50
Difference in volume between the affected and unaffected limbs — %	15.0±14.7	17.3±16.6	0.49
Common Toxicity Criteria lymphedema grade — no. (%)†			0.25
0	5 (7)	7 (10)	
1	18 (25)	12 (17)	
2	32 (45)	26 (37)	
3	16 (23)	25 (36)	

* Plus-minus values are means ±SD.

† Common Toxicity Criteria grades were defined following the guidelines of Cheville et al.¹⁷ Grade 0 lymphedema was defined as a difference in volume or circumference between the two limbs of less than 5% at the point of greatest visible difference, without swelling or obscuration of anatomical architecture. (We enrolled patients with grade 0 lymphedema only if they had written documentation of a previous diagnosis and treatment of lymphedema of grade 1, 2, or 3 by a certified lymphedema therapist.) Grade 1 lymphedema was defined as a difference in volume or circumference between the two limbs of 5 to 10% at the point of greatest visible difference or swelling or obscuration of anatomical architecture on close inspection or pitting edema. Grade 2 lymphedema was defined as a difference in volume or circumference between the two limbs of more than 10 to 30% at the point of greatest visible difference or readily apparent obscuration of anatomical architecture, obliteration of skin folds, or readily apparent deviation from normal anatomical contours. Grade 3 lymphedema was defined as a difference in volume between the two limbs of more than 30% at the point of greatest visible difference or lymphorrhea, gross deviation from normal anatomical contours, or interference with activities of daily living.

Table 2. Strength, Anthropometric, Diet, and Physical-Activity Data at Baseline and 12 Months, According to Study Group.*

Variable	Baseline			12 Mo			% Change between Baseline and 12 Mo					
	Weight Lifting no. with data	mean ±SD	P Value	Control no. with data	mean ±SD	P Value	Weight Lifting no. with data	mean ±SD	P Value	Control no. with data	mean ±SD	P Value
Bench press, maximum (lb)	70	43±16	0.21	70	39±13	0.21	56	53±18	<0.001	63	39±12	<0.001
Leg press, maximum (lb)	70	182±64	0.09	68	162±58	0.09	59	232±66	<0.001	63	165±57	<0.001
Weight (kg)	71	82.4±16.6	0.18	70	79.4±17.6	0.18	65	80.0±15.6	0.66	65	79.0±16.9	0.66
BMI†	71	31.0±6.2	0.21	70	29.9±6.6	0.21	65	30.0±5.7	0.70	65	29.9±6.5	0.70
Body fat (%)	71	40.1±5.7	0.42	69	39.5±5.2	0.42	65	39.6±6.3	0.90	65	39.9±5.3	0.90
Fat mass (kg)	71	33.3±10.3	0.27	69	31.8±10.6	0.27	65	32.0±10.1	0.87	65	31.9±10.5	0.87
Lean mass (kg)	71	50.3±7.7	0.29	69	49.1±7.7	0.29	65	49.1±7.3	0.63	65	48.4±7.5	0.63
Diet (kcal per day)	70	1835±1319	0.36	67	1610±1131	0.36	60	1532±679	0.08	63	1348±632	0.08
Physical-activity level (MET-min/wk)‡	54	1954±2423	0.49	61	2339±2589	0.49	52	2397±2548	0.20	57	1740±1935	0.20

* To convert bench and leg press values to kilograms, multiply by 0.45359. MET denotes metabolic equivalent.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

‡ The percent changes over the 12-month study period were calculated from natural-log-transformed physical-activity levels to improve the normality of the distribution.

(Table 2). Changes in diet, physical activity and anthropometric measures over the 12-month period were not significantly different between the two groups.

There was no significant difference between the two groups in the proportion of women who had a change in limb swelling of 5% or more (Table 3). This result did not materially change when the analysis was repeated without any imputed data from participants who were lost to follow-up (results not shown). Among the 130 women who had no second primary or recurrent cancers and were not lost to follow-up, 23 in the control group and 20 in the weight-lifting group were evaluated for exacerbation. Of these, 19 and 9 participants, respectively, were found to have had an exacerbation (83% vs. 45%). The total number of treatment sessions for exacerbation was 195 in the control group, as compared with 77 in the weight-lifting group. The number and severity of symptoms reported decreased more in the weight-lifting group than in the control group. No significant differences were noted between the two study groups with regard to self-reported adherence to prescribed lymphedema self-care therapies (results not shown). Post hoc analyses that excluded participants with grade 0 lymphedema yielded results similar to those reported in Table 3 (results not shown). Adjustment for baseline variables (cancer stage, number of nodes removed, race, physical activity, diet, and body-mass index) did not materially alter these results. There were no serious adverse events related to the intervention.

DISCUSSION

Contrary to common guidelines to avoid lifting with the affected limb, we found that weight lifting did not significantly affect the severity of breast cancer-associated lymphedema (as assessed by the primary outcome, an absolute increase of ≥5 percentage points in the interlimb volume difference). In addition, weight lifting reduced the number and severity of arm and hand symptoms, increased muscular strength, and reduced the incidence of lymphedema exacerbations as assessed by a lymphedema specialist.

Several previous studies, including a case series³³ and small randomized, controlled trials,³⁴⁻³⁷ have also suggested that weight lifting is safe for breast-cancer survivors with lymphedema. The

Table 3. Lymphedema Outcomes at 12 Months, According to Study Group.*

Variable	Weight Lifting		Control		Cumulative Incidence Ratio or Mean Difference (95% CI)†	P Value‡
	no. of patients with data	value	no. of patients with data	value		
Change in interlimb volume difference						
≥5% increase — no. (%)	70	8 (11)	69	8 (12)	1.00 (0.88 to 1.13)	1.00
≥5% decrease — no. (%)	70	13 (19)	69	15 (22)	0.96 (0.81 to 1.14)	0.68
Mean interlimb volume discrepancy between baseline and 12 mo (percentage points)	70	-0.69±5.87	69	-0.98±7.31	-0.29 (-1.94 to 2.51)	0.80
Exacerbation — no. (%)	65	9 (14)	65	19 (29)	0.47 (0.23 to 0.97)	0.04
Change in no. of symptoms reported between baseline and 12 mo§	70	-1.81±2.16	69	-1.17±1.94	-0.63 (-1.32 to 0.06)	0.07
Change in severity of symptoms between base- line and 12 mo§	70	-0.51±0.80	69	-0.22±0.71	-0.29 (-0.54 to -0.03)	0.03

* Plus-minus values are means ±SD.

† The mean difference is given for the weight-lifting group as compared with the control group for the difference in interlimb volume discrepancies (the interarm difference over time) and changes in number and severity of symptoms. The cumulative incidence ratio is given for the weight-lifting group as compared with the control group for differences in percentages.

‡ P values were calculated with the use of Fisher's exact test for between-group comparisons of percentages and the Wilcoxon rank-sum test for between-group comparisons of the difference in interlimb volume discrepancies and changes in number and severity of symptoms.

§ Data were reported by patients regarding 14 symptoms: rings too tight, watch too tight, bracelets too tight, clothing too tight, puffiness, knuckles not visible, veins not visible, skin feels leathery, arm feels tired, pain, pitting, swelling after exercise, difficulty writing, or other. The change in severity of symptoms is the mean of the changes in severity for all 14 symptoms, with the possible severity score for each ranging from 0 (no symptom) to 4 (very severe).

current trial was larger and of longer duration than those previously reported and also differed by testing a weight-lifting protocol with no upper limit on the resistance level to which participants could progress. A strength of this trial is its delivery in community fitness centers, primarily YMCAs, by trainers employed by these fitness centers. We adopted this approach with the goal of dissemination of the weight-lifting program if it proved effective. The ongoing LIVESTRONG at the YMCA program (a collaboration of the YMCA and the Lance Armstrong Foundation) includes the protocol described here as an intervention that can be offered to cancer survivors in YMCAs across the United States. Additional strengths of the present trial are the inclusion of a racially diverse population with a wide range of time since diagnosis (1 to 15 years) and the high rate of follow-up.

There are also potential limitations of the study. Evaluations for exacerbations were not completed by a single therapist, although the six lymphedema therapists assessing exacerbations followed a standardized algorithm for evaluation and had completed the 135-hour course recommended by the National Lymphedema Network.¹⁸

Therapists were unaware of which patients had been assigned to the weight-lifting group, as specified in the study design, but some participants in this group may have disclosed their recent weight lifting during evaluations for perceived exacerbations. Though the number of women evaluated for exacerbation was approximately equal in the two groups (23 in the control group and 20 in the weight-lifting group), the proportion of evaluated women who were found to have had an exacerbation was higher in the control group. One possible explanation for this observation is that some assessors may have become aware of the study-group assignments, resulting in biased assessments. However, the finding that symptom severity improved more in the weight-lifting group than in the control group supports a benefit of the intervention. An alternative explanation is that participants in the weight-lifting group, concerned about the potential for worsening of lymphedema with weight lifting, were more likely to seek care in the absence of objective evidence of exacerbation.

Although reporting bias cannot be ruled out as a possible explanation for the decrease in confirmed lymphedema exacerbations, several phys-

iological effects of exercise might alternatively explain these findings. There is evidence that exercise enhances the flow of lymph^{38,39} and improves protein resorption⁴⁰ and that the increased pulmonary work associated with exercise assists with lymph flow.⁴¹ It is also possible that increased muscle strength reduces the relative effect of common daily stresses to the limb.

The substantive treatment-related increases in strength, coupled with the lack of change in lean mass, indicate that the program was more focused on building muscle strength than on hypertrophy, as intended. Further research is needed to determine the critical components of this intervention in order to facilitate its optimal use by breast-cancer survivors with lymphedema.

In conclusion, the results of this study reduce concerns that weight lifting will worsen arm and hand swelling associated with lymphedema in breast-cancer survivors. These findings support the potential benefits of a slowly progres-

sive weight-lifting program in women with breast-cancer-related lymphedema, in conjunction with appropriate use of compression garments and close monitoring for arm and hand swelling.

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