Weight Lifting for Women at Risk for Breast Cancer–Related Lymphedema
A Randomized Trial

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Context  Clinical guidelines for breast cancer survivors without lymphedema advise against upper body exercise, preventing them from obtaining established health benefits of weight lifting.

Objective  To evaluate lymphedema onset after a 1-year weight lifting intervention vs no exercise (control) among survivors at risk for breast cancer–related lymphedema (BCRL).

Design, Setting, and Participants  A randomized controlled equivalence trial (Physical Activity and Lymphedema trial) in the Philadelphia metropolitan area of 154 breast cancer survivors 1 to 5 years postunilateral breast cancer, with at least 2 lymph nodes removed and without clinical signs of BCRL at study entry. Participants were recruited between October 1, 2005, and February 2007, with data collection ending in August 2008.

Intervention  Weight lifting intervention included a gym membership and 13 weeks of supervised instruction, with the remaining 9 months unsupervised, vs no exercise.

Main Outcome Measures  Incident BCRL determined by increased arm swelling during 12 months (≥5% increase in interlimb difference). Clinician-defined BCRL onset was also evaluated. Equivalence margin was defined as doubling of lymphedema incidence.

Results  A total of 134 participants completed follow-up measures at 1 year. The proportion of women who experienced incident BCRL onset was 11% (8 of 72) in the weight lifting intervention group and 17% (13 of 75) in the control group (cumulative incidence difference [CID], −6.0%; 95% confidence interval [CI], −17.2% to 5.2%; P for equivalence = .04). Among women with 5 or more lymph nodes removed, the proportion who experienced incident BCRL onset was 7% (3 of 45) in the weight lifting intervention group and 22% (11 of 49) in the control group (CID, −15.0%; 95% CI, −18.6% to −11.4%; P for equivalence = .003). Clinician-defined BCRL onset occurred in 1 woman in the weight lifting intervention group and 3 women in the control group (1.5% vs 4.4%, P for equivalence = .12).

Conclusion  In breast cancer survivors at risk for lymphedema, a program of slowly progressive weight lifting compared with no exercise did not result in increased incidence of lymphedema.

Trial Registration  clinicaltrials.gov Identifier: NCT00194363

JAMA. Published online December 8, 2010. doi:10.1001/jama.2010.1837 www.jama.com
that deconditions the arm, increasing the potential for injury, overuse, and, ironically, lymphedema onset. Adherence to these precautions may limit physical recovery after breast cancer and, for some women, result in lost employment. Furthermore, activity avoidance may deter survivors from performing regular exercise, which may prevent cancer recurrence and improve survival. By contrast, controlled physiological stress through progressive weight lifting may increase the maximal physical work capacity of the affected arm, protecting it from injury.

In a pilot study, we found no evidence that slowly progressive weight lifting precipitated lymphedema among breast cancer survivors, although that study had limited statistical power and follow-up. The Physical Activity and Lymphedema (PAL) trial was conducted among breast cancer survivors to determine whether exercise is safe for women at risk for lymphedema. Women were randomized to a 1-year weight lifting intervention group or a 1-year nonintervention group. The PAL trial was a single study statistically powered to address 2 distinct primary goals. We previously published the findings of the first primary goal, which was to assess the effects of weight lifting on lymphedema worsening. Herein, we report the results of the second primary goal, which was to evaluate incident lymphedema from weight lifting from a distinct pool of PAL participants.

**METHODS**

**Study Participants**

Breast cancer survivors with and at risk for lymphedema were recruited throughout the Philadelphia metropolitan area. Participants were recruited between October 1, 2003, and February 2007, with data collection ending in August 2008. Recruitment methods included letters sent by Pennsylvania and New Jersey state cancer registries, media advertisements and interviews, and flyers at support groups. After baseline measurements that confirmed whether women had lymphedema, participants were randomized into the trial about lymphedema worsening (results of which have already been published), or into the trial described herein, which evaluated incident lymphedema from weight lifting. Eligibility requirements for the trial included female sex, history of unilateral nonmetastatic breast cancer diagnosis between 1 and 5 years before study entry, body mass index (calculated as weight in kilograms divided by height in meters squared) of 50 or less, currently cancer free, no medical conditions that would limit participation in exercise, no weight lifting in the year before study entry, no plans for surgery or to be away for at least 1 month during the study, currently weight stable and not actively trying to lose weight, at least 2 lymph nodes removed, no prior lymphedema diagnosis, and no evidence of current lymphedema. For the purpose of eligibility, lymphedema was defined as an interlimb difference of at least 10% as measured by water volumetry, greatest circumferential difference, or, per the Common Toxicity Criteria version 3.0 adverse events criteria, swelling or obscuration of anatomic architecture or pitting edema. Women with suspected lymphedema were sent for evaluation with a certified lymphedema therapist (CLT) to verify eligibility. The FIGURE shows the 154 participants who entered the PAL trial at risk for lymphedema.

Women were placed into 2 equally sized groups through a computerized process called minimization in a manner that was unpredictable and concealed from research staff who determined eligibility. This approach balanced important potential confounders at baseline: age (<54 vs ≥54 years), number of lymph nodes removed (<6 vs ≥6), obesity (body mass index <30 vs ≥30), and history of radiation treatment (yes vs no). The study was approved by the University of Pennsylvania institutional review board. Women provided written informed consent and written clearance from a physician before participation.

**Intervention**

Participants in the weight lifting intervention group received a 1-year membership to a community fitness center (usually a YMCA) near their homes. For the first 13 weeks, women were instructed twice weekly on safe performance of exercises in groups of 2 to 6 survivors. Certified fitness professionals employed by the fitness centers led
these 90-minute sessions. Upper body exercises (seated row, supine dumbbell press, lateral or front raises, bicep curls, and triceps pushdowns) were performed with dumbbells or variable resistance machines. Lower body exercises (leg press, back extension, leg extension, and leg curl) were performed with variable resistance machines. The specific equipment used varied across the fitness centers at which the intervention was delivered. Three sets of each exercise were performed at each session, 10 repetitions per set. After 13 weeks, participants continued twice weekly unsupervised exercise to 1 year. Weight was increased for each exercise by the smallest possible increment after 2 sessions of completing 3 sets of 10 repetitions with no change in arm symptoms. Fitness trainers called women who missed more than 1 session per week throughout the year. Participants who missed more than 2 consecutive sessions were asked to reduce resistance and rebuild as per protocol above. Participants in the control group were asked to not change baseline level of exercise during study participation and were offered a 1-year fitness center membership with 13 weeks of supervised instruction following study completion. Further details of the intervention are provided elsewhere.20

All trainers who worked with participants underwent a 3-day training course including the exercise protocol and an overview of lymphedema prevention, symptoms, and treatment.21-23 An intervention coordinator met with trainers weekly during the first 13 weeks, then monthly to ensure protocol fidelity. All participants (weight lifting intervention and control groups) who developed lymphedema were provided a custom-fitted compression garment (Jobst, BSN Medical, Charlotte, North Carolina) and were required to wear these garments during weight lifting sessions. Trainers asked about changes in symptoms weekly and took circumference and water volume measurements monthly to ensure arm swelling changes were detected and treated promptly. In addition, all participants (weight lifting intervention and control groups) were required to attend a 1-hour educational lecture about lymphedema risk reduction, treatment, and exercise safety based on position stands from the National Lymphedema Network.17,22,24

Measurement
Measurements of all participants at baseline and 12 months were completed by trained staff using standardized methods. Measurement staff (including CLTs) were blinded to treatment allocation. Participants were reminded not to reveal their group assignment before measurement and evaluation sessions.

Demographic characteristics (age, education, race, occupation) were self-reported at baseline. Cancer stage was taken from the state cancer registry, surgical pathology report, or self-report, according to data availability. Treatment history was self-reported for radiation and chemotherapy. The number of lymph nodes removed was collected from surgical pathology reports. Anthropometry measures included weight, height (baseline only), and whole-body dual-energy x-ray absorptiometry scan (Hologic Discovery, software version 12.4, Bedford, Massachusetts). Percentage of body fat is presented without bone mass to avoid misrepresenting changes in relative fat mass due to changes in bone density. Physical activity outside of weight lifting was assessed using the International Physical Activity Questionnaire.25 Diet was assessed using the Diet History Questionnaire.26

The primary outcome was lymphedema onset defined as a 5% or more increase in arm swelling, which was defined by interlimb water volume difference ([affected arm volume–unaffected arm volume]/unaffected arm volume).27 Water volume displacement was used to measure arm volumes at baseline and 12 months.27 Water volume is accurate by raters to 1% and was taken once per side.28 For clinician-defined onset, CLTs17 at Penn Therapy and Fitness used a standardized clinical evaluation based on the Common Toxicity Criteria version 3.0 criteria,16 including interlimb differences, and changes in tissue tone or texture, as well as symptoms. Participants were sent for evaluation of possible onset upon report of a change in symptoms lasting 1 week or longer or if monthly preexercise safety measurements by fitness trainers or 3-month interval measurements by measurement staff indicated a change in treated arm volume of at least 5% and at least 5% interlimb difference. Lymphedema-related arm symptoms presence and severity were reported using a validated and reliable survey for detecting prevalent lymphedema.29

Strength measurements at baseline and 12 months provided physiological evidence of intervention adherence and strength gains. The maximum amount of weight that can be lifted once (1 repetition maximum=1-RM) was assessed for the bench press and leg press. One-RM tests, the standard for evaluating increases in muscular strength,30 are safe for most populations when properly supervised.30-32 Methods for the strength measurements have been reported elsewhere.20 Intervention adherence was also evaluated by attendance logs completed by fitness trainers.

Statistical Analysis
All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina). Descriptive statistics for baseline variables included rates for binary variables and means, medians, and SDs for continuous variables. The rates of occurrence of lymphedema and other binary outcomes were compared between the exercise and control groups using Fisher exact test and continuous outcomes were compared using the Wilcoxon rank sum test, with 2-sided \( P<.05 \). Cumulative incidence ratios (relative risks) of outcomes are shown with 95% confidence intervals (CIs).

Because clinician-defined onset required follow-up for 12 months, patients who were not evaluated due to recurrent cancer (5 in the weight lifting intervention group and 2 in the control group) or patients who dropped out of the trial (n=13) were excluded from this analysis. Simple im-
putation-based sensitivity analyses were conducted to examine the potential effect of these missing data on results. First, all dropouts were assumed to have had the event in question and then to not have had the event. For continuous lymphedema outcomes (eg, arm swelling and symptoms), data were imputed using a regression model, incorporating baseline covariates that predicted the outcome at \( P \leq .25 \), and properly incorporated patient-specific variability.

Sample size calculations were based on the primary comparisons of interest. The PAL trial had 2 primary comparisons of interest. The PAL trial assessed outcomes in 2 independent subgroups of women, those with and without lymphedema at baseline; each subgroup was designed with 80% power to show equivalent lymphedema onset between the weight lifting intervention and control groups, allowing up to a 20% loss to follow-up. Given these parameters, the trial sought to recruit at least 144 women at risk for lymphedema to detect more than a doubling of the rate of lymphedema onset, with an assumption that the background rate among the control group would be 6%. Furthermore, we planned a subgroup analysis among women who had 5 or more nodes removed. This threshold was chosen to be consistent with our prior work and published accounts that the majority of sentinel lymph node biopsies involve removal of 1 to 4 nodes.

### RESULTS

Table 1 shows the 154 randomized PAL trial participants at risk for lymphedema at baseline, including the 7 (4.5%) who had recurrent cancer and the 13 (8.4%) who were lost to follow-up. Participants were aged 36 to 75 years at baseline and diverse regarding education, race/ethnicity (29% nonwhite), and occupation. The number of lymph nodes removed ranged between 2 and 26, with a mean of 8 in the weight lifting intervention group and 9 in the control group; 94 women had at least 5 nodes removed. Interlimb differences in arm volume ranged between −11% and 13% (comparing affected with unaffected limb), with a mean of 0.13% and −0.27%, respectively, in weight lifting intervention and control group women.

Table 2 shows baseline and 12-month data for strength, anthropometry, and diet and physical activity. At baseline, the range for the 1-RM bench press test was 0 to 80 lb and the range for the leg press was 65 to 345 lb. Participants in both groups were well-balanced at baseline on strength and anthropometrics. Women in the weight lifting intervention group became stronger compared with the no exercise group. Percentage body fat was lower among the weight lifting participants at 12 months. Median attendance was 79% among the 77 women in the weight lifting intervention group, including the 13 lost to follow-up. No between-group differences were noted in dietary intake or self-reported physical activity outside of weight lifting at 12 months.

Table 3 shows lymphedema onset outcomes at 12 months. The proportion of women who experienced a 5% or more increase in interlimb volume difference during the 12 months was 17% (13 of 75) in the control group and 11% (8 of 72) in the weight lifting in-
tervention group (cumulative incidence difference [CID], −6.0%; 95% CI, −17.2% to 5.2%; P for equivalence = .04; cumulative incidence ratio [CIR], 0.64; 95% CI, 0.28-1.45; P for equivalence = .003; the upper limit of the CI is below the a priori equivalence boundary of 2 for the CIR). These results are based on imputed data for intention-to-treat analyses; findings were robust with repeated analysis without imputation. Among the 134 women at risk for lymphedema who had no new or recurrent cancers and not lost to follow-up, there were 4 incident cases of clinician-defined lymphedema (1 in the weight lifting group and 3 in the control group), producing a CIR of 0.34 (95% CI, 0.04-3.22; P for equivalence = .12). Sensitivity analyses (assuming the women lost to follow-up all had no events or all had events) resulted in CIRs that did not substantively alter the results. No notable differences in the number or severity of symptoms were observed in the weight lifting and control groups.

In planned secondary analyses limited to women with 5 or more nodes removed, the proportion of women who...
experienced a 5% or more increase in interlimb volume during the 12 months was 7% (3 of 45) in the weight lifting group and 22% (11 of 49) in the control group (CID, −15.0%; 95% CI, −18.6% to −11.4%; P for equivalence = .003; CIR, 0.30; 95% CI, 0.09-1.00; P for equivalence = .001). No between-group differences were observed in clinician-defined lymphedema onset or symptoms in secondary analysis limited to women with 5 or more nodes removed.

**COMMENT**

Breast cancer survivors who performed slowly progressive weight lifting twice weekly for 1 year were less likely to experience clinically significant increases in arm swelling than women in the control group. The majority of breast cancer survivors do not have lymphedema; however, they alter the use of their arms and upper body activities out of fear of developing lymphedema. The findings from our trial should help clarify clinical advice to patients who have completed breast cancer treatment regarding the safety of resuming or beginning a weight lifting program. These results are consistent with the well-defined hormetic effect of exercise training—small, slowly progressive increases in physiological stress buffer the body's ability to respond to infection, inflammation, and injury through gradual adaptations to muscle mass, metabolic demand on tissues, altered microcirculation, reduced oxidative stress, and improved inflammatory profile.

Prior randomized trials of weight lifting safety among breast cancer survivors, all of which agree with the current findings, have been smaller, shorter, and some have included lymphedema as a secondary outcome. Studies in Norway and Spain have demonstrated that when upper body exercise is combined with other lymphedema therapeutic modalities, no increased risk of onset is conferred or lymphedema may be prevented. Our study is the first well-powered clinical trial to our knowledge to demonstrate no increased risk of lymphedema onset with weight lifting alone, with the possibility of reduced likelihood of increased arm swelling among higher risk women with 5 or more nodes removed.

Strengths of the PAL trial include the large sample size and the delivery in community fitness centers, primarily YMCAs, by trainers employed by these fitness centers. This approach was purposeful, with a goal of increasing the likelihood of broad dissemination. Additional strengths include the participant diversity (29% nonwhite participants), long intervention (1 year), and minimal loss to follow-up (8.4% of women did not have recurrent cancers). Limitations included marginal significance of a treatment effect on lean mass. Changes in lean mass were more favorable in women in the weight lifting group vs the control group during the 12-month trial (−0.45 vs −1.47 kg, P = .06), but it is unclear why there were decreases in lean mass on average given the notable increases in strength (and in contrast with findings from the pilot study). Multiple elements of the PAL trial intervention were specifically designed to reduce the risk of lymphedema onset. First, breast cancer survivors started with 13 weeks of supervision to learn to perform the exercises properly and to progress the resistance appropriately. Second, participants started training at a low weight (1 or 2 lb) and progressed resistance according to symptom response. If there was a break in exercise that lasted 1 week or more, the protocol specified that the resistance should be reduced and increased gradually. It was vital to the participants' sense of safety that there were CLTs available to whom they could be referred. These intervention elements are in keeping with the National Lymphedema Network position statement on exercise and the American College of Sports Medicine guidance for exercise in breast cancer survivors. Third, all fitness trainers were certified by a national organization and underwent training about the specific exercises used, adaptations that might be required, and when and whom to call if there were symptoms or measurement changes that might require medical evaluation.

In conclusion, the findings of our study remove concerns that slowly progressive weight lifting will increase risk of lymphedema onset in breast cancer survivors. In a preplanned secondary analysis limited to women with 5 or more nodes removed, the incidence of 5% increase in arm swelling was reduced by 70% among women in the weight lifting intervention group compared with no exercise. No between-group differences were noted for clinically defined lymphedema onset or symptom changes in the total cohort or this higher-risk subset. The primary goal was to test safety of weight lifting, not superiority; therefore, additional research is needed before concluding that weight lifting prevents lymphedema. However, even with the finding of no harm, our results combined with previously published results for women with breast cancer–related lymphedema suggest that the many health benefits of weight lifting should now become available to all breast cancer survivors.

**Published Online:** December 8, 2010. doi:10.1001/jama.2010.1837

**Author Contributions:** Dr Schmitz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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*Financial Disclosures:* None reported.

*Funding/Support:* This work was supported by grant R01-CA106851 from the National Cancer Institute (Dr Schmitz) and by the Public Health Services Research grant RR024134 from the National Institutes of Health to the University of Pennsylvania. In addition, BSN Medical provided in-kind support in the form of custom–fitted compression garments and the fitness centers where the weight lifting intervention was delivered discounted membership fees for study participants (YMCA of Philadelphia and Vicinity; Sisters in Shape, the Family YMCA of Burlington County, New Jersey, and the Community YMCA of Eastern Delaware County).
Role of the Sponsors: None of these funding sources had any role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

Additional Contributions: We thank the lymphedema therapists at Penn Therapy and Fitness who evaluated and treated the participants in this study, including Joy C. Cohn, PT, CLT-LANA; Nicole L. Dugan, PT, DPT, CLT-LANA; Bernadette Enskon, PT, CLT-LANA; Rebecca Maurer, DPT, CLT-LANA; Beth Anne Morris, MSPT, CLT-LANA; Nancy Stewart, PT, MEd, MPT, CLT; and Bryan Spinelli, PT, MS, OCS, CLT. All of these lymphedema therapists were compensated for their work on the PAL trial. We also thank the paid staff of the PAL trial at the University of Pennsylvania, including Amy Rogerino, MPH (recruitment and data management), and Darnali Mason, MS (measurement). The exercise protocol, including progression in which the exercises were taught, is available upon request.

REFERENCES

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