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Physical Activity and Lymphedema (The PAL Trial): Assessing the safety of progressive strength training in breast cancer survivors

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Abstract

Lymphedema is a chronic and progressive long-term adverse effect of breast cancer treatment commonly defined by swelling of the affected arm. Current clinical guidelines indicate that women with and at risk for lymphedema should protect the affected arm from overuse. In clinical practice, this often translates into risk averse guidance to avoid using the arm. This could lead to a disuse pattern that may increase the likelihood of injury from common activities of daily living. Further, such guidance poses an additional barrier to staying physically active, potentially translating to weight gain, which has been shown to be associated with worse clinical course for women with lymphedema. We hypothesize that a program of slowly progressive strength training with no upper limit on the amount of weight that may be lifted would gradually increase the physiologic capacity of the arm so that common activities represent a decreasing percentage of maximal capacity. Theoretically, this increased capacity should decrease the risk that daily activities put stress on the lymphatic system of the affected side. The Physical Activity and Lymphedema (PAL) Trial is a recently completed randomized controlled exercise intervention trial that recruited 295 breast cancer survivors (141 with lymphedema at study entry, 154 at risk for lymphedema at study entry). The purpose of this report is to provide detail regarding the study design, statistical design, and protocol of the PAL trial.

Keywords

lymphedema; exercise; breast cancer

Introduction

It is estimated that over 200,000 women in the US will develop breast cancer (BrCa) in 2008, making it the most prevalent cancer diagnosis in American women [1]. Until recently BrCa research has focused on treatment measures to optimize survival; this research has been

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successful, as 5-year survival is approximately 86% for all stages combined [1]. Increasing attention is now being devoted to the unique health issues BrCa survivors face, including increased risk of BrCa treatment-induced chronic disease and morbidity that affect function and quality of life, such as lymphedema [2]. Lymphedema is often characterized by swelling of the arm, shoulder, neck or torso on the side of the body where a woman had treatment [3], and develops due to physical disruption or compression of the lymphatic channels from surgical resection and/or radiation-induced fibrosis of lymphatic vessels or nodes [4]. Treatment-induced damage interrupts lymph transport such that lymph volume exceeds transport capabilities [4], eventually leading to abnormal accumulation of tissue protein, edema, and chronic inflammation within the arm [5]. The associated swelling may range from mild and barely noticeable to extremely noticeable and disabling [6]. These physiologic changes may result in decreased range of motion and function, decreased muscle strength, and the need to alter choice of clothing and several activities of daily living including household duties, sleep, employment, and leisure time physical activity [7]. Physiological morbidities include increased risk of infection, including cellulitis, fibrosis, compartment syndrome and lymphangiosarcoma (Stewart-Treves syndrome) [4]. Physical morbidities include skin changes [6], loss of sensation and limb function, as well as pain of varying intensity and frequency [4]. Significant psychosocial morbidity, depression, and social inhibition have all been described in association with lymphedema [7-13]. BrCa survivors may find lymphedema more distressing than mastectomy as it is less possible to hide the physical manifestation and loss of arm function that negatively affect many aspects of daily life [6]. Lymphedema is a chronic disease that may be managed, but is unfortunately without a cure [6].

The prevalence of lymphedema varies by source, case definition, and length of follow-up. For example, the prevalence is estimated at 49% when including self-reported symptoms of lymphedema [6,14]. In contrast, estimates as low as 6% have also been reported [3]. Surgical approaches such as sentinel node biopsy have led to reduced incidence of lymphedema [15]. However, one recent study reported that despite availability of newer surgical approaches, the risk of lymphedema remained a key concern with an incidence rate of nearly 17% at twelve months post-surgery among women who underwent a sentinel node procedure [15].

Lack of knowledge about lymphedema and the lymphatic system makes it difficult to predict who will develop lymphedema [12]. Petrek et al. [14] described 20 possible post-treatment risk factors for lymphedema from a 20-year prospective cohort study of 272 women treated with mastectomy and complete axillary dissection. In accord with previous studies, [16,17] arm infection and injury, as well as elevated body mass index (BMI), were significantly associated with lymphedema development in this cohort [14]. By contrast, other commonly described potential risk factors including air travel, prolonged carrying of heavy objects, and compression did not increase risk in this cohort [14]. Occupational and leisure time physical activity (light, moderate and vigorous) are clinically accepted but unsupported by longitudinal research as possible risk factors for the development of lymphedema [14]. The clinical acceptance of physical activity as a risk factor for the development or worsening of lymphedema is easy to understand, even in the absence of empirical support. Certainly, it appears unwise to over-stress a lymphatic system that has been compromised by node removal and/or radiation therapy. Unfortunately, that wisdom is sometimes translated into avoidance of using the affected arm. This may translate into reduced functional ability of the arm through disuse. We hypothesized that carefully controlled increase of muscular strength and endurance might be preferable to women over-stressing their musculoskeletal and lymphatic systems during inevitable activities of daily living that require vigorous upper body work, such as carrying children or groceries, shoveling snow, or carrying a heavy suitcase.

There have been several smaller intervention trials of upper body exercise in BrCa survivors; results regarding lymphedema risk are encouraging [18-21]. For example, data from 81

survivors in the Weight Training for Breast Cancer Survivors study indicate that six months of progressive strength training with no upper limit on the amount of weight lifted does not lead to any greater incidence of lymphedema onset or flare-ups (worsened symptoms) compared to a concurrent randomly allocated control group [22]. Empirical evidence that it is safe for BrCa survivors with or at risk for lymphedema to perform carefully designed programs of progressive upper body strength training would be helpful for promoting health among survivors. BrCa survivors are at increased risk for diabetes, osteoporosis, fatigue, decreased quality of life, and weight gain resulting from BrCa treatment [23-29]. These complications impair the physical functioning of BrCa survivors for years after treatment completion [30]. Strength training protects against and/or attenuates each of these conditions [31-49].

A well-powered, well-designed randomized controlled intervention is needed to allay fears that upper-body exercise is a risk for lymphedema onset or flare-ups in BrCa survivors [50]. The premise of such a trial is that as women get stronger in a carefully controlled setting, activities of daily living that previously may have overstressed the musculoskeletal system, and thereby the lymphatic system, would represent an increasingly lower percentage of maximal strength and endurance, and would be less likely to result in lymphedema onset or flare-ups. If it can be established that BrCa survivors can safely engage in progressive strength training, the potential health benefits of this mode of physical activity will become available to this growing population. The recently completed Physical Activity and Lymphedema (PAL) trial was designed to address this need. The study design of the PAL trial is described herein.

Trial design and methods

Overview & Specific Aims

The primary aim of the PAL trial was to assess the safety of twice-weekly progressive strength training, including arm exercises, in breast cancer (BrCa) survivors 1 to 15 years post-diagnosis of BrCa. A comparison between a group randomly assigned to the exercise intervention and a group of non-exercising controls included the following safety outcomes: 1) rates of lymphedema incidence among women who entered the study without lymphedema and 2) rates of flare-ups (worsening of lymphedema) among women who entered the study with lymphedema. Secondary aims included comparison of multiple secondary outcomes related to lymphedema, quality of life, and expected physiologic changes with strength training between groups. By design, the safety of strength training will be evaluated in equal sized strata of BrCa survivors with and without lymphedema. This study was designed to establish the safety of this intervention in two distinct groups of BrCa survivors: those *with* and those *at risk for* lymphedema. It was hypothesized that rates of incident lymphedema and of flare-ups in the strength-training participants would not be higher than the background rates for the non-exercising control participants. Additional adequately powered aims included assessment of changes in: physical functioning of the arms, muscular strength, body composition, bone density, blood glucose levels, health-related quality of life, sleep, fatigue, self-esteem, optimism, life satisfaction, sexual function, body image, social support, and general quality of life. It was hypothesized that breast cancer survivors who participate in strength training would experience improvements in each of these outcomes, compared to controls. All study activities were reviewed and approved by the University of Pennsylvania Human Subjects Protection Programs. All participants signed an informed consent document prior to any study activities. In addition, participants were required to provide written physician's clearance prior to completing any study activities.

Inclusion and exclusion criteria

The inclusion/exclusion criteria for PAL were designed to balance three goals: recruitment feasibility, excluding those for whom the risks of the intervention outweigh the potential

benefits, and the ability to test study hypotheses. Eligible participants were female breast cancer survivors 1 to 15 years post-diagnosis among those *with* stable lymphedema and 1-5 years post-diagnosis for those *without* lymphedema at study entry. Eligible women were free of cancer at study entry and had had at least 1 lymph node removed. For the purpose of study eligibility, stable lymphedema was defined as one of the following conditions: 1) $\geq 10\%$ inter-limb discrepancy in volume or circumference at the point of greatest visible difference OR swelling or obscuration of the anatomic architecture on close inspection OR pitting edema; 2) a prior clinical diagnosis of lymphedema and having had any prior intensive lymphedema therapy on the affected arm. If a woman self-reported a clinical diagnosis of lymphedema and study measurements indicate $< 10\%$ inter-limb discrepancy, no swelling or obscuration of the anatomic architecture on close inspection, and no pitting edema, written verification of the diagnosis from a qualified clinician was required for study entry. In addition, all four of the following conditions had to be met for eligibility among women with lymphedema: 1) no intensive therapy within the past three months (intensive therapy is defined as complex decongestive therapy provided by a qualified lymphedema therapist); 2) no recorded 10% change in volume or circumference of the affected arm in the last three months that has lasted seven days or more; 3) no more than one lymphedema-related infection requiring antibiotics (cellulitis) within the past 3 months; and 4) no change in Activities of Daily Living (ADLs) due to a lymphedema exacerbation for the past 3 months. Further, to ensure that those with interlimb differences greater than 20% were truly stable, water volumetry measurements were repeated at baseline with 2-4 weeks between measurements. Those with affected limb changes of greater than 5% between repeated baseline measurements were excluded from the study (this never occurred). In cases of questionable eligibility regarding whether a potential participant had stable lymphedema, Dr. Cheville and the lymphedema therapists at Penn Therapy and Fitness were consulted.

Non-lymphedema related eligibility criteria included: no medical conditions or medications that would prohibit participation in an exercise program or would negatively affect the ability to test primary aims; body mass index ≤ 50 kg/m²; no plans for surgery (e.g., reconstructive) during the study period; no history of bilateral lymph node dissection (because this would prohibit the ability to assess the primary outcome of interest); not planning to move away from the area over the next year; not pregnant or lactating or planning to become pregnant during the study; among women who have given birth: at least 6 months post-pregnancy and at least 3 months post-lactation; no strength training or other upper body resistive or aerobic exercise within the past year; and willingness to be randomized (women not willing to be randomized did not have access to the intervention). Women involved in moderate to vigorous cardiorespiratory fitness activities were not excluded from this study. While this inclusion could potentially reduce the power to detect effects in several secondary outcomes, it increased feasibility of recruiting BrCa survivors and was not thought to alter the ability to test primary hypotheses.

Sample size and power for an equivalence hypothesis

The *a priori* goal was to recruit and randomize 288 women, 144 with and 144 without lymphedema. Power calculations were based on two *a priori* primary equivalence hypotheses: 1) there would be no difference in the incidence of lymphedema flare-ups (worsening) across treatment status among those who entered the study with lymphedema AND 2) there would be no difference in lymphedema incidence across treatment status in those who entered the study without lymphedema. Equivalence hypotheses require an *a priori* definition of what is considered a clinically meaningful difference between groups so that the study would be adequately powered to show that any difference smaller than a specified threshold is NOT significant, to support the primary hypotheses. Decisions regarding what constituted a clinically meaningful difference and the equivalence threshold were made upon consultation

with multiple clinicians in the area of lymphedema care regarding what would be an important shift in interlimb change within woman that should constitute a flare-up or onset, as well as the difference in proportion of onsets and flare-ups that would result in the clinicians choosing to recommend that their patients avoid weight-lifting (expert opinion). Among women with lymphedema at baseline, a sample size of 60 per group provided 80% power to test equivalence, where lack of equivalence was defined as a 20% or greater increase in the expected background rate of 10% lymphedema flare-ups over 12 months (based on chart reviews of several lymphedema therapists), using a one-sided test with a significance level of 0.05. Among women who entered the study without lymphedema, a sample size of 60 per group provided 80% power to detect equivalence, where lack of equivalence was defined as a doubling of the expected background incidence rate of 6% for lymphedema onset in the control group over 12 months (based on data from the pilot study), again using a one-sided test with a significance level of 0.05. Both sample sizes were inflated by 20% to 72 per group to account for possible drop outs. Effect sizes for all secondary outcomes range from 0.33 to 0.50 for n=60 per group. Because of the large number of secondary outcomes, a modified Bonferroni correction procedure will be applied to maintain appropriate experiment-wise Type I error rates. Analysis of primary and secondary endpoints will be repeated after stratification by duration of post-diagnosis survival to discern whether effects vary by time since diagnosis.

Definitions of Flare-up and Onset

No information was found in the peer-reviewed literature to indicate an empirical cut point to define a flare-up in women diagnosed with lymphedema secondary to breast cancer. The flare-up definition provided below was developed in consultation with lymphedema clinicians who assisted with the trial. Evaluation for possible flare-ups took place at Penn Therapy and Fitness by trained lymphedema therapists who were blinded to treatment status to determine whether a given participant required medical treatment at that time. For the purpose of the study, a participant was considered to have had a flare-up only if the evaluating therapist determined that treatment was needed. There were two possible triggers for flare-up evaluations: 1) women could request an evaluation at any time during study participation based on a change in symptoms that lasted a week or longer and 2) if measurements by research staff (blinded to treatment status) indicated a 5% increase in inter-limb difference, accompanied by a 5% increase in affected arm when compared to the last measurement time point OR baseline. An objective measure of flare-ups was also included: 5% increase in inter-limb difference comparing 12 month to baseline data.

The definition for onset used for the PAL trial is consistent with the Common Toxicity Criteria Adverse Event version 3.0 for grade 1-2 lymphedema [51]. Onset of lymphedema is defined as the new development of a $\geq 10\%$ inter-limb discrepancy in volume or circumference at the point of greatest visible difference or swelling or obscuration of anatomic architecture on close inspection, or pitting edema, and confirmation of onset by a lymphedema therapist who is blinded to treatment status. Evaluation for onset could also occur at the request of a participant who had new symptoms that lasted a week or longer or as a result of changes noted by measurement staff (with a threshold for evaluation that was the same as for flare-ups).

Recruitment and screening

Recruitment took place between October 2005 and February 2007 in waves, according to the geographic location of the participating fitness centers. All but one of the intervention fitness centers were within local Young Men's Christian Association (YMCA) facilities. Locations were chosen based on density of survivors residing within one zip code of the fitness center (pre-determined by state cancer registry data) as well as the ability of a specific fitness center to assist with the trial (e.g., interest and available staff). Recruitment of an ethnically diverse study population was supported by including two fitness intervention sites located in primarily

African-American neighborhoods in Philadelphia. All interested women were screened by phone; eligible and interested women were scheduled for consent sessions. Additional details of recruitment and screening procedures are provided elsewhere [52].

Randomization: Minimization to balance across a large number of potential confounders

Participants were enrolled in the study in 11 recruitment waves ranging in size from 7 to 40 women. Within each wave, participants were assigned in equal numbers to the intervention group or to the control group using a process called minimization [53,54] in a manner that was unpredictable and concealed from those who determined eligibility. All measurement staff remained blinded throughout the study. The choice of minimization was motivated by the large number of potential confounding variables on which it was important to achieve balance at baseline. In this scenario, stratified, blocked, blinded randomization was infeasible. A meeting of investigators early in the planning process led to the conclusion that although randomization stratified by lymphedema status (diagnosed versus not diagnosed) would be sufficient for inferential purposes, greater sensitivity should be sought by also balancing the groups on time since diagnosis (up to 5 years versus more than 5 years), current age (< 53 versus \geq 53 years), body mass index (BMI, < 30 versus \geq 30 kg/m²), history of radiation therapy as part of breast cancer treatment (yes versus no), number of lymph nodes removed as part of breast cancer surgery (<6 versus 6 or more), and inter-limb differences (affected arm <10%, 10-20%, or >20% larger than unaffected arm). Each of these variables is hypothesized to be associated with the development of and/or clinical course of lymphedema [14,15,55], and thus, may be associated with intervention risks and success. Minimization was achieved using a software program (MINIM, version 1.5) [53], into which de-identified data for each of the above variables were entered. This was done after completion of all baseline measures, the study coordinator then called participants to reveal the outcome of randomization and to schedule groups for the supervised groups. The program was set to balance groups on each of the above variables with equal weighting. Balance was checked for the full cohort after every wave was allocated to groups. There were never any concerns as to whether the process was resulting in balance across all factors. Results in Table 1 show that this process succeeded in producing balance on each of these factors at baseline.

Intervention: Delivered in the community by YMCA fitness trainers

The first treatment group supervised intervention sessions started in March 2006; the last wave of treatment group supervised intervention sessions started in June 2007. Social cognitive theory [56] formed the theoretical basis for the PAL intervention. Elements of social cognitive theory incorporated into the PAL intervention and evaluation included reciprocal determinism, behavioral capacity, expectations, self-efficacy, modeling, and reinforcements [56]. PAL trial intervention elements (and associated evaluation methods) are described according to how they fit into these concepts in Table 2. All interventionists for the PAL trial were employees of the facilities in which the intervention took place. Qualifications included fitness trainer certification from a National Committee for Certifying Agencies accredited organization, such as the American College of Sports Medicine, and successful completion of all 24 hours of trainer training specifically for the PAL intervention protocol (delivered by KH Schmitz at each of the eight participating fitness centers specifically for staff at that particular location). Those randomized to the treatment group were offered the 12 month intervention immediately after randomization, while those randomized to the control condition were offered the intervention after a 12-month delay. Participants attended twice-weekly strength training sessions for 12 months, supervised in small groups of 2-6 for the first 3 months, and then unsupervised for the remaining 9 months. The fitness trainers remained available to the treatment group participants during the unsupervised portion of the intervention and called participants if more than one consecutive session was missed in order to encourage adherence to the exercise protocol. Additionally, fitness trainers were available by phone and email, as

well as for individual personal training sessions up to once monthly. Participants received monthly or bi-monthly reminders of the availability of these resources through email and/or telephone contact. We chose a frequency of 2 rather than 3 weekly sessions because a review of prior strength training studies did not reveal greater fat free mass (FFM) increases from 3 sessions [57-60] compared to 2 sessions weekly [45,61,62] and to improve behavioral feasibility.

Each session took 60-90 minutes and began with a 10-minute cardiovascular exercise warm-up, followed by brief range of motion stretching of the major muscle groups to be worked during strength training. Then participants performed 5-15 minutes of exercises intended to strengthen spinal stabilization muscles and deep abdominal muscles as well as increase awareness of body-mind connection. These 'core training' exercises were included in the protocol for the purpose of injury prevention during strength training. Participants also did stretching at the end of each session for injury prevention purposes. During the latter stretching session, each stretch was held for at least 30 seconds.

Nine common strength-training exercises were performed using variable resistance machines and free weights (for muscles of the chest, back, shoulders, quadriceps, hamstrings, and gluteals, as well as biceps and triceps). The protocol for determining resistance differed for the upper versus the lower body. For the upper body, participants started with no weight or one pound weights for each exercise. If there were no changes in symptoms or onset of lymphedema-related symptoms by the next week, the weight was increased by one-half to one pound increments. If there was any worsening/onset of symptoms, the exercise thought to be associated with the symptoms was skipped, or a lighter weight was used, until the symptoms cleared up. A set of one-half pound wrist weights, as well as two pairs of dumbbells in 1 pound increments (up to 10 pounds) were purchased for each of the intervention facilities. For the lower body, a standard progressive strength training approach was used in which participants lift the most weight they can lift in each exercise eight to ten times in each set of repetitions. Participants build up to three sets per exercise over the first 3-4 weeks of exercise. For the lower body, substitute exercises were used if injuries or excessive soreness occurred, or if there were range of motion limitations that precluded performing a specific exercise. For the first three months, the protocol for increasing weight on each 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 possible increment. If the higher weight was lifted at least eight times on the first set, and six times on the second set, additional set(s) was attempted with the higher weight. Otherwise, the weight reverted to the amount lifted in the previous session. For the nine months of unsupervised training, participants increased the weight after 4 sessions during which the participant lifted the same weight for 10, 10, and 12 repetitions for sets 1, 2, and 3, respectively. A key element of the intervention to ensure safety of participants was careful monitoring to ensure that if a woman missed enough sessions that deconditioning may have occurred (2 or more sessions), the trainer would provide guidance to back off on the resistance used and gradually increase the weights on the same schedule noted above.

One essential element of this intervention was ongoing safety measurements to ensure that if there were changes in arm swelling or symptoms requiring evaluation by a lymphedema specialist for possible onset/flare-up, it was discovered and responded to in a timely manner. Therefore, in addition to the exercise intervention, participants 1) were asked weekly if they had any change in symptoms that have lasted a week or longer and 2) underwent monthly arm measurements, performed by the trainers. Measurements included water volumetry and 4 circumference measurements (at the metacarpal phalangeal joint, as well as 8 and 20 and 44 cm proximal to the metacarpal phalangeal joint). The process evaluation measurements were not compared to the outcome measurements taken by blinded measurement staff and were used

solely for the purpose of determining whether there was any cause for evaluation of possible onset/flare-up of lymphedema. Upon the discovery of a change in symptoms or swelling that has lasted a week or more, the study coordinator contacted the participant and an evaluation appointment was scheduled with the lymphedema therapists at the University of Pennsylvania. All participating lymphedema therapists had completed the training recommended by the National Lymphedema Network for qualified specialists [63].

Participants in exercise intervention studies often ask about nutritional changes once the study starts. PAL participants were instructed to allow normal seasonal variability in diet over the year of study participation, but to not make any purposeful changes in diet that might result in gain or loss of body weight/fat. This restriction enables us to test the effects of exercise, rather than a combination of strength training and diet changes. If further nutritional guidance was requested, participants were guided to a USDA website (www.mypyramid.gov).

Intervention compliance

There are two distinct groups that received aspects of the PAL intervention: the trainers and the participants. As agents of social influence, trainers received training related to implementing a weight-training program for BrCa survivors: building self-efficacy in participants through self-monitoring, goal setting, and increasing performance attainments; enhancing social support for the participants by facilitating the establishment of social networks between participants; and communication skills. The trainers also needed to be well versed in the strength training protocol for the study, signs and symptoms of lymphedema, and ongoing process evaluation and safety monitoring of arm symptoms and measurements. The interventionist training took place within an intensive 3-day workshop, led by Dr. Schmitz. An intervention coordinator met with the trainers weekly at each intervention site during the supervised portion of the intervention and monthly thereafter, to review whether the trainers were calling participants who missed sessions and to discuss any challenges encountered by the trainers who were delivering the intervention. Participants kept their exercise logs at the fitness facility and were called by their trainer if they miss more than one scheduled exercise session to encourage them to make up the session. Participants were provided with a water bottle for completing the first three months of supervised training, a gym bag for completing six months of training with at least 80% attendance, and a pair of weight lifting gloves for completing months six to 12 with at least 80% attendance. If travel, vacation, or a significant life event (e.g., major medical event, birth or death in the family) prohibited participation for a period of one week or more, an arrangement was made in advance to not make these phone calls for an agreed-upon amount of time. The tone of the phone calls to non-adherent participants was positive, encouraging, empathetic, and non-confrontational. Calls were generally short, with a brief statement by the participant describing when she planned to do her next exercise session and/or what specific life event kept her from completing an exercise session and discussion of when she would be able to return. These methods to promote intervention compliance appeared to be successful. Median attendance to weight-lifting sessions was 88% in 70 treatment group women who entered the study with lymphedema, including the five women who were lost to follow-up. Among 72 treatment group women at risk for lymphedema, including the six who were lost to follow-up, median attendance was 79%.

Study Retention and participant compensation

In addition to approaches to promoting compliance to the exercise intervention among the treatment group, multiple approaches were taken to retain PAL participants in the study over 12 months for the purpose of measurements. These approaches, for all study participants (treatment and control groups), included providing every participant with a T-shirt with the study logo at the completion of baseline measurements; periodic mailings to update the

participants on press attention to the ongoing study; birthday cards; holiday greeting cards; and a 'Celebrate Survival' event featuring lunch, motivational speakers, and a fashion show. A total of 34% of participants who had been randomized at the time of the event attended. Every communication with participants had an underlying tone that 'Together, we're making things better for future breast cancer survivors.' Participants were compensated with \$50 for completing measurements at baseline and 12 months and \$15 for measurements at 3, 6, and 9 months. Free parking was available for consent sessions, measurement visits, and exercise sessions. Further, all women with lymphedema received custom fitted compression sleeves and gauntlets (e.g. gloves without fingertips) at baseline and 6 months into the study, regardless of group assignment. Women in the control group received a third compression sleeve and gauntlet at 12 months to enable them to participate safely in the intervention at the end of study participation. Finally, any woman, regardless of treatment or control status, who had a change in symptoms in her arm or torso that lasted a week or longer that was suspected to be related to lymphedema, was seen by a qualified lymphedema specialist for a free medical evaluation. Several times during the study, mailings were sent to all participants to remind them of the availability of free lymphedema evaluation and treatment, in addition to the quarterly reminders at measurement time points. If the therapist indicated that complex decongestive lymphedema treatment was required, it was paid for by the study, regardless of the number of sessions needed.

Study measures at baseline, 3, 6, 9, and 12-month follow-up

All measurements were taken by trained research staff who were blinded to participant treatment status. All measures were taken at baseline and 12 months, with few exceptions. A subset of measurements was also taken at 3 and 6 months. At 9 months, participants were called to ask if they had had a change in symptoms or swelling of their affected arm that lasted a week or longer over the prior 3 months. If the answer was yes, a flare-up report form was completed and an appointment for evaluation of lymphedema onset/flare-up was scheduled with the lymphedema specialists at the University of Pennsylvania. Every time lymphedema-related physical measurements were made, participants were given specific instructions to control for alcohol, water, and caffeine intake and to avoid vigorous activity for the 48 hours prior to measures. Lymphedema compression garments were removed 1 hour prior to all measures.

Primary outcome: limb volume by water displacement combined with clinical assessments

Often considered the "gold standard" for measuring limb volume, water volumetry is based on Archimedes' Principle that states that the water volume displaced is equal to the volume of the object immersed in the water [64]. Participants sit for testing and the water is "tepid or cool" [65]. Water volume is accurate by raters to 1% and only need be measured once [66]. However, lymphedema onset and flare-ups are not just defined by changes in swelling of the affected limb. Changes in tissue tone and texture are also important indicators of onset and flare-up. These were evaluated by the lymphedema therapists at Penn Therapy and Fitness at baseline and twelve months as outcome measures and at each evaluation measurement appointment using standardized measurements recorded on a form developed specifically for the PAL trial.

Additional outcomes and measures

Lymphedema related

Circumferential measurements: Circumferential measurements were assessed at baseline, 3, 6, and 12 months. The participant was placed in a supine position and starting just distal to the metacarpal-phalangeal (MCP) joints, measurements were taken circumferentially every 4 centimeters (baseline and 12 months) or every 8 centimeters (3 and 6 months).

Bioelectrical spectroscopy (BIS): Lymphedema is characterized by excess protein-rich extracellular fluid in the affected limb. When applied at multiple frequencies and with proper electrode placement, bioelectrical impedance analysis can distinguish between intra- and extracellular body water in specific body segments. The differences in the electrical properties of intra- versus extracellular waters result in prevention of electrical current passing through the intracellular water at low currents. By passing a current through the body at multiple frequencies, it is therefore possible to separate intra- from extracellular fluid volumes in the arm. The measurement was done on the affected and unaffected arm to determine a ratio that is highly sensitive to changes in extracellular water. Impedance measures have been found to be reliable, with week-to-week coefficients of variability of 2.2% on repeated measures [67]. This methodology has been shown to be fourfold more sensitive to edema changes in limbs than circumferential volume measures [68]. All participants underwent BIS measurements at baseline and 12 months. BIS involved placing electrodes on the wrists and feet of the participant and passing a small electrical current through the body. Placement of electrodes was as per published guidance to ensure that the focus would be on impedance within one arm at a time [69,70]. Briefly, two measurement electrodes were placed at either end of a 40 cm long segment of the arm, with current drive electrodes placed approximately 10 cm distally. Identical electrode positions were used on both arms. MFBIA measurement on each arm was performed using a SFB7 multiple frequency bioimpedance monitor (Impedimed, San Diego, CA). Impedance of the extracellular fluid for each limb calculated using the manufacturer's software. The ratio of these values comparing the treated and untreated sides of these women with unilateral breast cancer (unaffected arm:affected arm) was calculated.

Pain: Ratings have been determined to be reliable and valid using the Visual Analogue Scale from 0 to 10 [71-73]. The area of pain was documented along with the sensation (throbbing, aching, dull), duration and frequency, and extent to which the symptoms interfered with aspects of daily life. The pain questions were revised from the Brief Pain Inventory [74] based on investigators prior clinical experience with arm symptoms in breast cancer survivors.

Self-reported lymphedema symptoms: Self-reported lymphedema symptoms were assessed with a survey that has previously been shown to have a specificity of 0.90 and sensitivity ranging from 0.86 to 0.92 for diagnosing lymphedema (defined as difference in circumferences of greater than 2 cm) when compared to clinical assessment by a physical therapist with special training in lymphedema [75]. The survey also included a listing of 14 symptoms that, if endorsed, were also rated as to severity and frequency.

Lymphedema onset/flare-up moderators: There are reported risk factors for lymphedema onset and flare-ups that are commonly asked about in clinical evaluations, which have varying degrees of empirical support. These risk factors include: fever, vigorous exercise in hot humid weather, sunburn, pet scratch, insect bite, cut, hang nail, manicure, blister, hot tub use, travel by airplane, acupuncture on affected arm, bruise to affected arm, change of breast prosthesis, venipuncture on affected arm, bra too tight, blood pressure cuff used on affected arm, constriction of affected arm by poor fitting clothing or jewelry, lying or sleeping on affected side, surgery, travel to a different altitude, heavy lifting, overuse of arm from chores or occupational activity, menstrual changes, sauna use, infection in affected arm, sports injury to affected arm, skin burn to affected arm, more alcohol intake than usual, large seasonal change (e.g., barometric pressure, humidity, and temperature change). Participants evaluated for onset or flare-up of lymphedema were asked about these possible risk factors, and any specific precipitating event was recorded. Additionally, the extent to which BrCa survivors with diagnosed lymphedema follow professional advice for symptom prevention/progression was also recorded on a survey developed for this study.

Additional upper body function testing—The Nine Hole Peg Test of Finger Dexterity was used to measure coordination. Scores from this assessment can be rated against participants themselves or against adult norms. This test has been found to be reliable and valid [76]. Range of motion measurements were taken on both upper extremities using standard procedures with a goniometer and include the following joints: shoulder (flexion, extension, internal and external rotation); and elbow (supination, pronation) [77]. Grip strength was also assessed with a handheld dynamometer, 3 trials per hand.

Other physiologic outcomes

Body composition: Body fat (percent and total), fat free mass, and bone density were measured by dual energy x-ray absorptiometry (DeXA) in the total body scanning mode with a Hologic DeXA apparatus (Hologic, Inc., Bedford, MA). In addition, lower spine and hip scans were performed to evaluate the effect of strength training on bone density in these important regions. Fasting blood draws occurred 48+ hours after the most recent exercise session. Glucose was measured immediately with a Beckman glucose analyzer. Body weight and height were assessed using a calibrated digital scale and a scale-mounted stadiometer.

Muscle strength testing: The maximum amount of weight that can be lifted once (1 Repetition Maximum = 1 RM) was assessed for the bench press and the leg press. One RM tests are the standard by which increases in muscular strength are evaluated [78] and have been found to be safe for most populations when properly supervised, including our pilot study in breast cancer survivors [78-80]. After a five minute cardiorespiratory exercise warm-up, and familiarization with the leg press, participants rated the difficulty (1 to 10, with 10 most difficult) of a warm-up set of 4-6 repetitions (40 lbs. on leg press, five lbs. on bench press). Participant difficulty rating was used to choose the first weight at which a 1 RM test was attempted. Resistance was added until exercise biomechanics were altered in a manner that might lead to injury or the participant was unwilling or unable to try a heavier weight. In addition, for the bench press, participants were asked to evaluate their arm symptoms after each lifting attempt and stop upon symptom change.

Survey measures

Quality of life measures: Long-term breast cancer survivors experience the double burdens of common age-related chronic health problems and the sequelae of their cancer or cancer treatment. Some sequelae may be physiologic, others psychological. Some, like fatigue, may be a combination of both. It was hypothesized that the PAL intervention would reduce some of these burdens and potentially enhance feelings of well-being. The effects of disease and its treatment, assessed by the patient, are commonly termed quality of life (QOL) or more precisely, health-related QOL [81]. To measure the impact of the PAL intervention on patient reported outcomes, QOL measures at baseline and at one year were compared between exercise and control groups. One review observed that many intervention studies in BrCa survivors have had limited success with health-related QOL measures [82]. These authors suggested that for future studies to be effective they should: 1) include questions about body image symptoms (including arm symptoms), and 2) develop specific modules by the addition of a small number of items (with appropriate validation) to existing validated multi-dimensional questionnaires. With this guidance in mind, the PAL investigators developed a *Health and Attitudes Survey* as the main QOL data collection tool. This survey is a battery of standardized instruments, selected because they are conceptually consistent with the constructs identified in the literature on outcomes of exercise or proposed by pilot data, have admirable psychometric properties including responsiveness to change, are readily scored and interpreted, may be self-administered, and are appropriate for adults across a broad spectrum of health states. The survey took about 30 minutes to complete, 84% (N=249) of the 295 randomized participants completed all the quality of life surveys at baseline and at the twelve month follow-up time point.

The PAL study participants are relatively healthy women, seeking greater well-being and increased function. Therefore, the *Health and Attitudes Survey* included measures salient to persons living at home and able to perform basic activities of daily living. The selected measures were intended to be sensitive to improvements at the higher levels of health, such as moving from inability to perform vigorous exercise to engaging in vigorous activities. The core of the survey was the SF-36, Version 2 [83], the most widely used generic health profile. It is appropriate for use with adults of all ages, and has extensive age- and gender-specific norms. Further, it has been used extensively in breast cancer survivors [84-86]. To augment the SF-36 core, a few highly salient concept-specific measures evaluated fatigue, sleep dysfunction, self esteem, optimism, life satisfaction, sexual function, body image, and perceived social support. References for the survey instruments included in the PAL trial are provided in Table 3.

The impact of BrCa on sexual function and body image has been a focus of much research, often using measures developed by the authors for a particular study. Less studied have been the issues of sexual relationships and body image in BrCa survivors with lymphedema, resulting in a need to develop tools specifically for this group of survivors. Data demonstrate that sexual problems do not tend to resolve within the first year or two of disease-free survival [87,88]. During the first few years of the PAL trial, study investigators developed a scale to measure sexual relationships and body image in the survivors [89]. The instrument demonstrated excellent test-retest reliability and convergent validity.

Physical activity: Physical activity outside the prescribed exercise sessions was assessed by self-report using the long-form self-administered version of the International Physical Activity Questionnaire, which as been found to be both valid and reliable in multiple populations [90].

Dietary assessment: Dietary intake was measured to ensure that any observed intervention effects on the primary outcomes of interest were not the result of concomitant dietary intake changes. To assess usual food and nutrient intake a food frequency questionnaire [91] was self-administered. Validation studies indicate that the DHQ outperforms the Block and the Willett questionnaires in women [92].

Demographic data was collected via a self-administered survey regarding ethnicity, education, marital status, number and ages of children living in the home, and employment status. Menstrual history and illness/injuries were assessed using surveys developed for the pilot study. Medical record abstraction was performed by a nurse abstractor for all participants to ensure accurate recording of the specifics of the breast cancer diagnosis (stage, grade, histology, etc.) and treatment (surgeries, chemotherapy agents, radiation, hormonal therapy, etc.). The abstraction form was based on experiences of collecting similar data from the pilot participants, as well as ongoing studies of colleagues at the University of Pennsylvania.

Qualitative data collection (exit interviews with treatment group participants): Our past experience showed that participants frequently told trainers of the benefits that they were realizing as part of the weight training program and, as part of our process data collection in the pilot study for the PAL trial, trainers documented the myriad comments from participants. Such qualitative feedback is an important aspect of capturing the experiences of participants and, combined with quantitative outcome data, adds richness and context to the research findings. Participants may also share information useful for dissemination of the PAL trial intervention. For the PAL trial, we systematically collected qualitative data from women by conducting focus groups with treatment group participants to ask about the positive and negative aspects of the intervention and how they would improve the program. These interviews were conducted by non-intervention staff and audio-taped. Qualitative data analysis techniques will be used to interpret and summarize the findings [93].

Data safety and monitoring

The data safety monitoring plan for the PAL trial focused on close monitoring by the principal investigator (PI) in conjunction with a safety officer, along with prompt reporting of excessive adverse events and any serious adverse events to the NIH and to the IRB at the University of Pennsylvania. Safety monitoring reports were produced by the study coordinator. The injury/illness survey form completed at 12 months met some of the goals of this plan. An adverse events reporting form was developed specific to the PAL trial, based on the pilot study experience. Safety reports were sent to the study statistician, the PI, the safety officer, and several lymphedema specialists who agreed to consult on the grant. The frequency of data review for this study is summarized as follows: participant accrual (adherence to protocol regarding demographics and inclusion/exclusion) was summarized after randomization of each recruitment wave; adverse event rates (injuries, lymphedema onset or flare-up) were reviewed as they occurred and summarized quarterly; stopping rules regarding lymphedema onset or flare-ups were reviewed quarterly. Finally, attendance (compliance with treatment) and drop-out rates were reviewed semi-annually.

Data analysis

All analyses will be stratified by baseline lymphedema status (stratum). Data description will consist of presenting means, together with numbers, standard deviations, quantiles, and ranges, at each of two primary measurement points (baseline and 12 months later), separately by experimental condition. Histograms will be used to assess whether the assumption of Gaussian distribution is reasonable. Waves will be compared on a range of variables to monitor comparability. The primary analyses will be the equivalence hypothesis tests of the safety endpoint, comparing rates of incident lymphedema and flare-ups of lymphedema between the strength-training group and the control group. The incidence rates will be reported within the treatment and control groups, within baseline lymphedema status, with 95% confidence intervals. A cumulative incidence ratio of 1.2 or greater, demonstrating at least 20% greater incidence of flare-ups among women with lymphedema at baseline would be cause to reject the primary study hypothesis of lack of harm of strength training among those women. A cumulative incidence ratio of at least 2.0, demonstrating a doubling of lymphedema incidence with strength training compared to women in the control group would be cause to reject the primary study hypothesis of equivalence of strength training and lack of strength training among women who entered the study without lymphedema. For the secondary endpoints, two-sided, two-sample t-tests will be used to compare the groups with respect to changes from baseline for volume-difference change and circumference-difference change; an adjusted Bonferroni procedure will be applied to address the issue of multiple comparisons. The simplest comparisons within lymphedema strata will use two-sample t-tests of mean changes from baseline to study end. More sensitive analyses will use general regression models to adjust changes for baseline characteristics such as baseline body mass index, and to examine associations between different endpoints and at interim measurement time points. The Statistical Analysis System (SAS, Version 9) will be used for analyses.

Lessons learned

There were many lessons learned in the process of carrying out the PAL trial, including issues surrounding ensuring patient compliance, acceptability and quality of data from surveys used, adequacy of safety procedures, and partnering with the YMCA. Methods for ensuring that the treatment group completed two exercise sessions weekly at the YMCA were based upon the success of similar methods used in the pilot study and appear to be successful (88% and 79% average attendance among treatment group women with and at risk for lymphedema, respectively). Though testing methods of exercise intervention compliance was not a goal of

this study, the success of the frequent personal contact and telephone follow-up approach described herein indicates that it may be useful for other studies as well.

There were also lessons learned in the area of questionnaire acceptability and the quality and the quantity of data from these surveys. Anecdotally, the survey participants reported disliking the most was the diet history questionnaire, which is quite long and detailed and took most participants over an hour to complete. Another issue with this survey is that, more than any other survey, confusion over the skip patterns on the survey resulted in the need to call women back when there was a logical inconsistency (e.g., never eats carrots, but serving size for carrots is 1-2 cups). There were many quality of life surveys included in the study, all chosen a priori as measuring constructs expected to change as a result of an exercise intervention. The variance in the number of participants who completed all surveys at both time points (N=249, 84% randomized) versus a subset of surveys at both timepoints (N=264, 89% randomized) is only 15 women or 5% of the randomized sample. From this we conclude that the number of surveys was not excessive. Planned analyses will examine which surveys are most informative and sensitive to change.

Interactions with clinicians familiar with lymphedema (physical medicine and rehabilitation physicians and certified lymphedema therapists) prior to initiating the study led to the comprehensive safety procedures used in the PAL trial. The monthly safety measurements at the YMCA with the fitness trainers were very well attended for the supervised portion of the study, and poorly attended thereafter (<50% of measurements completed, despite multiple attempts by trainers to complete measures at each time point). There was never a measurement from a fitness trainer that prompted follow-up for possible lymphedema onset or flare-up. Attendance at the three and six month in-person measurement visits with trained, blinded measurement personnel was 92 and 91%, respectively, which supports the idea that these measures seemed worthwhile to the participants. Further, the option to self-refer to a lymphedema therapist for evaluation of possible onset or flare-up after a change in symptoms of one week or longer was used by a total of 14% (N=41) of the 295 randomized participants on one or more occasion. There is tremendous fear of lymphedema in this population and methods to ensure women that safety was of utmost importance were viewed as being a high priority for the PAL trial. No one left the study due to onset or flare-up; this and the high retention of the cohort support the contention that we succeeded in assuring participants that their safety was of high importance to the study staff.

Finally, there were lessons learned in the area of partnering with the YMCAs. The fitness facilities with which we partnered varied in multiple characteristics, including the number of qualified personal training staff available to deliver the intervention, enthusiasm of staff to deliver a strength training intervention to breast cancer survivors, and staff with appropriate knowledge, skills, and abilities to organize this effort. Invested leadership at the level of wellness directors or even executive directors at any given facility did not appear to influence interactions at a given facility after the initial approval was obtained to work with the facility. The success or lack thereof of the PAL intervention in a particular facility rested mostly with the fitness trainers who directly delivered the intervention. A total of 17 fitness staff at 8 fitness facilities went through the intervention training with Dr. Schmitz. With only three exceptions, each trainer worked with his/her group for the full year of intervention, as originally intended. This was also true for the control groups. Weekly intervention staff meetings during the supervised sessions were planned for one hour and often ran long based on the volume of issues raised. These meetings were useful to the trainers to trouble shoot issues and for the research staff to make course corrections for trainers to follow the protocol. Monthly meetings with trainers appeared to make trainers aware that they needed to complete adherence, measurement, and symptom change process evaluation forms on a regular basis. There was one site at which these meetings were simply not possible based on the busy schedules of the three trainers

delivering the intervention. The amount of missing process evaluation data at this site was larger than for facilities where intervention staff meetings occurred as planned. All in all, it appears that it is possible to train YMCA fitness staff to safely deliver a weight training intervention to breast cancer survivors with and at risk for lymphedema.

Conclusion

The PAL trial intervention ended for the last recruitment wave in June 2008 and data collection was complete in August 2008. Results of this trial will be useful for shaping resistance exercise guidelines for breast cancer survivors with and at risk for upper body lymphedema. Placing the women into equal sized groups that are balanced by multiple potential confounders was successfully accomplished using minimization. The study was also successful in partnering with eight YMCA and other fitness facilities in the Philadelphia Metropolitan area to deliver a high quality intervention to breast cancer survivors. In doing so, many lessons were learned that may be useful to other researchers interested in using this model for delivering health behavior interventions in a community setting such as the YMCA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Intervention Sites

SIS Fitness: Melanie Merchand, Tasha Odom, Sandra Sasse; Philadelphia Area YMCA Association Office: John Flynn, Shannon Connolly, Linda Shock-Gloner; Main Line YMCA: Mary Francis Reilly, Claine Crew, Lisa Newman, Rashida Shoemaker; West Philadelphia YMCA: Gregory Lyles, Alonzo Holder, R. Kitt Walls; Ambler Area YMCA Wellness Center: Kathy Perry, Rachel Dubin, Holly Cutler, Janet Buthe, Jennifer Merrill, Gilda Smith; Mt. Laurel Branch YMCA: Serena Harris, Joann Agolia, Patricia Lawyer; Eastern Delaware County Community YMCA, Lansdowne Branch: Duane Johnson, Miriam Ranalli; Ridley Area YMCA: Debbie Mignogna, Colleen Greeley, Leslie Purtell, Nicole Juliano; Northeast Family YMCA: Paula Green, Donna Kim

University of Pennsylvania and Children's Hospital of Philadelphia: Carrie Stricker, CNRP, ONP, Angie DeMichele, MD, MSCE, Rebecca Smith, MD, Sandra Norman, PhD, Babette Zemel, Ph.D., Denise DePaul, Kimberly Fawver, Edward Ross, Jennifer Dagger, Jeffrey Muenzer, Rachel Meislin, Robert Andrew Diamond, Christina Smith, Elizabeth Helker, Shawn Fernandes, Quincy Greene, Maximilian Herlim, Jesse Chittams, Mamta Dubey, and Sandra Masiak

Penn Therapy and Fitness (lymphedema therapists and administrators): Andrea Branas, Joy Cohn, Brian Spinelli, Berandette Erikson, Nicole Dugan, Nancy Stewart, Linda Boyle, Elizabeth Croulet, Gina Burns, Mia Gonzales, Kim Grosch, Rebecca Golden

Other Lymphedema Therapists: Leslie Benson, Carrie Oatman McOskey, Linda Miller

BSN Medical, Inc.

Impedimed, Inc.

LympheDIVAS

PowerPads

Recruitment Assistance: Black Women's Health Alliance: Constance Sumner, RN, Jazmine Alavarez; Living Beyond Breast Cancer: Elyse Caplan, MA, Amy B. Grillo; Susan G. Komen Foundation Philadelphia Affiliate: Jennifer Leith; Linda Creed Foundation: Donna Dunkin; Fox Chase Cancer Center, Philadelphia PA: Wilma Morgan, Janice Buhler, Vicki Moran, Cheri Doll, Carolyn Weaver; Virtua Health System: Judy Neuman, Phyllis Duda, Doug Marshall, Barbara Francks, Eric Miller, Adrienne Kirby; Cancer Institute of NJ Cooper University Hospital: Ann Stephanie; Christine Hayes Physical Therapy: Tracy Harper; American Cancer Society: Carol Waties; Chestnut Hill Hospital: Amanda Zavodnick, J. Ehmman; Delaware County Memorial Hospital: Anne Matthews, Suzanne R. Smith, Deborah Markiewicz, Monica E. Smith, Rachele M. Lanciano, Linda S. Callans, Mark A. Rovito; Amy Davis; Villanova

University College of Nursing: Patricia K. Bradley; Mercy Hospital of Philadelphia: Kay Stevens; Christian Stronghold Baptist Church, Philadelphia, PA: Veronica Suber; Salvation Army: Stephanie Evans; The Wellness Community of Philadelphia: Karen Neyer; Breast Cancer Resource Center at the Princeton YWCA: Lia Daniels, Kara Stephenson; South Jersey Breast Cancer Coalition: Loretta Mikulski; National Black Leadership Initiative on Cancer: Ernestine Delmoor; Sisters Health Initiative: Janet Cash; Ardmore Presbyterian Church: Joanne Poorman; Women of Faith and Hope, Inc.: Novella K. Lyons; Rena Rowan Breast Center, Abramson Cancer Center of the University of Pennsylvania; New Jersey State Cancer Registry: Homer Wilcox III; Pennsylvania Cancer Registry: Robin Otto, Craig Edelman

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Table 1
Baseline values for characteristics used in the minimization (randomization) procedure (Mean (SD) or %)

	With Lymphedema		Without Lymphedema	
	Treatment N=71	Control N=70	Treatment N=77	Control N=77
Age (years)	56 (9)	58 (10)	54 (8)	56 (8)
Time since cancer diagnosis (months)	79 (45)	88 (45)	39 (15)	42 (16)
Body mass index (kg/m ²)	31.0 (6.2)	29.9 (6.6)	27.5 (5.1)	28.6 (6.2)
Number of nodes removed	16 (8)	16 (8)	8 (6)	9 (6)
Percent Interlimb difference	15.0 (13.7)	17.3 (16.6)	0.13 (5.1)	-0.27 (4.9)
Radiation treatment (% yes)	83%	76%	77%	75%

Table 2
Behavioral theory concepts as addressed by the PAL intervention and evaluation

Concept	Intervention	Evaluation
Reciprocal determinism	<ul style="list-style-type: none"> • Provided intervention in community settings close to participant's homes 	<ul style="list-style-type: none"> • Not evaluated
Behavioral capacity	<ul style="list-style-type: none"> • 13 weeks of supervised intervention with a qualified fitness professional to increase knowledge and skills for weight training • Lymphedema education session 	<ul style="list-style-type: none"> • Attendance at 13 weeks of session as predictor of longer term attendance and physiologic outcomes • Attendance at lymphedema education session
Expectations	<ul style="list-style-type: none"> • 13 weeks of supervised intervention with a qualified fitness professional to increase knowledge and skills for weight training • Regular contact (at least monthly) after the initial 13 weeks between trainers and participants for the remainder of the year to ensure expectations of the study and the participant were clear • Lymphedema education session 	<ul style="list-style-type: none"> • Outcome expectancies survey [94] • Focus groups to ask participants if their expectations were met
Self-efficacy	<ul style="list-style-type: none"> • 13 weeks of supervised intervention with a qualified fitness professional • Taught the nine weight training exercises over 8 sessions. Very gradual progression toward doing full exercise protocol to promote self-confidence 	<ul style="list-style-type: none"> • Sallis Exercise Self-Efficacy Survey [95]
Social support	<ul style="list-style-type: none"> • Small group training (peer-to peer support) • Trainer phone calls when participants missed calls (leader to participant support) • Regular contact (at least monthly) between trainers and participants after the initial 13 weeks 	<ul style="list-style-type: none"> • Sallis Exercise Social Support Survey [96]
Modeling	<ul style="list-style-type: none"> • Small group training so that most groups had at least one high attender (> 75% of sessions completed) 	<ul style="list-style-type: none"> • Ability to compare whether women with at least one small group member with high attendance were more likely to attend regularly as well
Reinforcements	<ul style="list-style-type: none"> • Incentives: water bottle at 3 months, gym bag at 6 months, weight training gloves at 12 months • PAL event: Celebrating Survival 	<ul style="list-style-type: none"> • Focus groups to assess whether participants liked the incentives and PAL event

Table 3
Quality of life and other survey measures used

<i>Quality of Life</i>
Pittsburgh Sleep Quality Index [97,98]
Relationship and Body Image [89]
Fatigue [99]
SF-36 Health Survey [100]
Coopersmith Self-Esteem Inventory [101]
Life Orientation Test [102]
Visual Analog Scale (QOL) [103]
Medical Outcome Study Social Support [104,105]
Temporal Satisfaction with Life Scale [106]
Depression Survey [107]
<i>Other</i>
International Physical Activity Questionnaire [90]
Diet History Questionnaire [91]
Demographics
Menstrual Tracking
Medical History