HHS Public Access

Author manuscript

Contemp Clin Trials. Author manuscript; available in PMC 2018 February 19.

Published in final edited form as:

Contemp Clin Trials. 2017 October ; 61: 63–72. doi:10.1016/j.cct.2017.07.017.

The women in steady exercise research (WISER) survivor trial: The innovative transdisciplinary design of a randomized controlled trial of exercise and weight-loss interventions among breast cancer survivors with lymphedema

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Abstract

Introduction—Breast cancer survivors face dual challenges: long term sequelae of treatment, and risk of recurrent disease. Obesity and a sedentary lifestyle complicate both challenges. The

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WISER Survivor trial assessed the effects of exercise and/or weight-loss on lymphedema, biomarkers of breast cancer recurrence, and quality of life. We report on the innovative transdisciplinary design of this trial and report attrition rates.

Methods—This one year trial randomized breast cancer survivors who had a BMI of ≥25 kg/m^2, were sedentary and had breast-cancer-related-lymphedema to 1) exercise (weight training and aerobic exercise) 2) weight-loss 3) exercise and weight-loss 4) or control group. Innovative aspects included: adaptation of a community-based weight training program to a largely home-based program; use of a commercial meal replacement system as part of the lifestyle modification weight-loss program; inclusion of measures of cost-effectiveness to enable economic evaluations; and alignment with a parallel mouse model for breast cancer recurrence to enable transdisciplinary research. In this model, mice bearing dormant residual tumor cells, which spontaneously relapse, were placed on a high-fat diet. Overweight animals were randomly assigned to exercise, calorie restriction, both, or control group and followed for cancer recurrence. The animal model will guide mechanistic biomarkers to be tested in the human trial.

Results & discussion—351 participants were randomized; 13 experienced breast cancer recurrence during the trial. Of the 338 participants without recurrence, 83% completed the trial. The WISER Survivor trial will show the effects of exercise and weight-loss on lymphedema outcomes, biomarkers of recurrence and quality of life.

NCT ClinicalTrials.gov registration #: NCT01515124

Keywords

Lymphedema; Biomarkers; Breast cancer; Relapse

1. Introduction

Breast cancer survivors face many challenges, typically divided into two broad categories: persistent adverse effects of treatment, and risk of recurrent disease [1]. The WISER Survivor trial was designed to address both challenges by assessing the effects of exercise and/or weight-loss on lymphedema (a persistent treatment effect), and biomarkers for recurrence. Additionally, it assessed effects on quality of life.

Breast cancer-related lymphedema incidence varies from 20 to 35% largely depending on whether patients are treated with sentinel lymph node biopsy or axillary dissection [2]. Lymphedema is associated with discomfort, depression, and disability, and compromises medical, social, functional, vocational, and psychological status [3–6]. Obesity increases the risk of breast cancer-related lymphedema [7–9]. Moreover, obesity and lymphedema may act synergistically to erode health-related quality of life [10–12].

Randomized trials demonstrated that upper body strength training is safe and increases muscular strength among survivors suffering from lymphedema [13,14]. Our group previously demonstrated that a twice-weekly slowly-progressive weight training program halved the incidence of clinical events that required medical care for lymphedema [15], but had no effect on the cardinal feature of lymphedema: arm swelling. Two small studies suggest that weight-loss can be beneficial with regard to lymphedema outcomes [16,17].

However, the combined effect of weight-loss and weight training on arm swelling has not yet been studied.

Large observational studies have consistently observed reduced breast cancer recurrence among women who are physically active, with maximal benefits seen for an amount of activity roughly equivalent to 30 min of walking per day [18,19]. In contrast, observational data on breast cancer recurrence and weight change are not fully consistent. For example, the Nurses' Health Study suggested that weight gain was associated with increased risk of recurrence, but the LACE cohort found no association [20,21]. Several large intervention studies in breast cancer survivors are currently ongoing to study the effect of weight-loss on breast cancer outcomes [22].

Previous studies in breast cancer survivors have examined the effects of exercise and weight-loss on mechanistic pathways [23–28], mainly focusing on insulin and insulin-like growth factors, inflammation, and the immune system. Based on research of mechanistic pathways in primary breast cancer, other pathways may also be potentially relevant [29,41–52]: these include those involving insulin resistance, growth factors and adipokines; sex steroid hormones; pathogenic angiogenesis; and inflammation/oxidative stress. So far few, if any, studies have examined effects on all potentially relevant pathways.

The WISER Survivor trial was designed to test the effects of exercise and/or weight-loss on lymphedema, biomarkers for recurrence and quality of life. The hypothesis is that exercise and weight loss will affect these outcomes, but that the combined effect will be larger. WISER Survivor was performed as part of the Transdisciplinary Research on Energetics and Cancer (TREC) initiative [29,30]. The Penn TREC Survivor center focused on three interwoven projects to span the translational research continuum from basic animal research through clinical research to economic evaluation and dissemination (Fig. 1). This setting signifies the unique features of the WISER Survivor trial: the alignment of a human trial with a parallel mouse study and an economic evaluation of the intervention. The current paper describes the innovative design and methods of the WISER Survivor trial, provides a description of baseline characteristics of participants, and reports retention rates.

2. Methods

2.1. Study population and recruitment

Eligible participants were female sedentary breast cancer survivors aged 80 years or younger with a BMI of ≥25 kg/m^2 with breast cancer-related lymphedema who had completed curative treatment at least six months prior to randomization and were currently free of cancer. Exclusion criteria were: grade 4 lymphedema, medical conditions or medications that would prohibit participation in an exercise program, inability to walk for 6 min unaided, extreme obesity (body mass index > 50 kg/m^2), plans for additional (e.g. curative or reconstructive) surgery during the study period, self-report of weight training within the past year, already engaging in 3 or more times weekly aerobic activity of moderate intensity (e.g. brisk walking, step aerobics or bicycling), planning to move away from the area over the next year, current use of weight-loss medication (OTC or prescription), self-report of alcohol or substance abuse within the past 12 months, including at-risk drinking (current

consumption of > 14 alcoholic drinks per week), and weight-loss > 10% of body weight in the past 3 months. In addition, we specified that participants experiencing a cancer recurrence (except for non-melanoma skin cancers) during the study would be removed from the study at the time of recurrence.

Recruitment strategies were targeted to increase the participation of racial/ethnic minorities as described earlier [31]. Over a 39-month period, participants were recruited through both active strategies such as community education events supplemented and passive approaches, such as mailings to survivors identified through hospital and state cancer registries.

2.2. Randomization and design of the interventions

WISER Survivor trial was a 12-month, four-arm, randomized controlled intervention trial. The four equally sized arms were: 1) exercise (weight training and aerobic exercise), 2) weight-loss through lifestyle modification, 3) both exercise and weight-loss and 4) control group. The primary aim was to determine the effect of the interventions on change in interlimb volume difference. The secondary aims were to assess the effects of the intervention on biomarkers of breast cancer recurrence and to assess effects of the interventions on health-related quality of life. An additional project leveraged the WISER Survivor study to assess cost-effectiveness of the three tested interventions. The trial was executed in 15 waves throughout a four year period; within each wave, women were assigned to one of the four groups in equal numbers, using the process of minimization [32]. Minimization ensures balanced groups over a set of possible confounding factors. We defined the following factors, each of which is hypothesized to be associated with the clinical course of lymphedema: baseline BMI (above or below BMI of 37.5 kg/m^2), age (above or below 65 years), radiation (yes or no), number of nodes removed (above or below 5), lymphedema severity (grade 1, 2, 3 or 4), and trunk edema only (yes or no). With a trial that was executed in waves, a stratified, blocked, blinded randomization was infeasible. We used the software program MINIM (MINIM, version 1.5) [53] for the minimization process. All measurement staff remained blinded throughout the study.

2.3. Exercise intervention: weight training and aerobic exercise

The exercise intervention combined a twice-weekly weight training intervention with 180 min per week aerobic exercise (mostly walking). The intervention was based on our earlier completed trials, which were mainly community-based [15,33–36]. In the current WISER Survivor trial, we adapted the intervention into a largely home-based setting, see Table 1 for an overview of the exercise intervention. The weight training was designed based on the PAL trial [15]. However, the PAL trial exercise program took place within fitness centers. Qualitative research from the PAL trial indicated that a home based program might be preferred by breast cancer survivors. A pilot study was undertaken that successfully translated the intervention to the home setting (unpublished data). Revisions to the PAL trial intervention to make it home based were also included in the physical therapy adaptation of the PAL intervention, called Strength After Breast Cancer [37]. This version of the intervention has now been documented to be equally effective for lymphedema outcomes [37] and is broadly disseminated (> 400 centers across the U.S.), given the availability of an online training to prepare allied health professionals to deliver the Strength After Breast

Cancer program [38]. Further, we included aerobic exercise as component of the exercise intervention to be able to study whether adding this component to the previously established, effective intervention for lymphedema of the PAL trial would have additional benefits on lymphedema outcomes and on biomarkers.

In weeks 1–6, participants were trained by certified fitness professionals on the weight training intervention and how to safely increase their aerobic exercise activity to 180 min per week; weight training was group-based. In addition, participants were instructed to do one unsupervised weight training session per week in weeks 1–6. Adjustable dumbbells (PowerBlocks, Inc., Owatanna, MN) were shipped directly to participants' homes upon randomization to an exercise group. Women were required to wear their compression garment during all weight lifting activities. They were not required to wear it during aerobic exercise.

During the first 6 weeks of the intervention, there were weekly group-based sessions to teach participants the exercise program. The group-based weight training sessions during the first 6 weeks of the intervention provided the participants with: instruction on basic weight training technique, and on the nine weight training exercises, documentation of exercise logs, review of accurate tracking procedures, and provided the contact information of the exercise physiologist for questions and concerns throughout the study.

Each supervised weight training session consisted of five parts:

1. A warm up session of at least 10 min at low to moderate intensity (brisk walking, bicycling or steps aerobics). Level intensity was defined as moderate using the Borg scale [39]
2. Stretching exercises for each of the major muscle groups, 15 s per stretch.
3. Core training exercises of abdominal and lower back muscles, including one stabilization, one flexion, and one extension core exercise ten repetitions per set per exercise.
4. Weight training exercises. No more than three weight training exercises were introduced per session; the full protocol was introduced over four weeks. Exercises included nine exercises: chest-presses, squats on a chair, one-arm rowing exercise, side-raises, step-ups, kickbacks, split-leg lunges, side lunges, and bicep-curls. Participants received an instruction booklet with color pictures of the exercises and things to remember when doing the exercises. Participants were instructed to perform the exercise in the order as instructed during the supervised sessions, to do two sets of ten repetitions for each exercise during the first month, and to add a third set per exercise starting in week 5 and for the remainder of the study. Participants were instructed to start with light weights and to increase the resistance by the smallest available increment (e.g. 1 lb) for each exercise when they could do three sets of the exercise with proper form for two consecutive sessions. If there were no changes in lymphedema-related or other symptoms, participants could follow this incremental progression. If there was worsening of lymphedema symptoms, the upper body exercises were

removed from the exercise program for a week until symptoms resolved. If there were musculoskeletal symptoms or other reasons why a person could not do a certain exercise, the exercise was skipped until symptoms resolved, or replaced with a different exercise that did not give symptoms if symptoms did not resolve.

5. Cool down consisted of stretching exercises for each of the major muscle groups for at least 30 s per side.

During weeks 7–52, participants were instructed to continue with the weight training using the same routine as during the first 6 weeks, including gradual progression of resistance. The home-based exercises during weeks 7–52 were unsupervised, with additional supervised monthly in-person sessions. Monthly in-person sessions consisted of a meeting with the fitness professional to address questions and concerns, and to provide behavioral counseling to improve intervention adherence and exercise-related behavior. According to the preference of the participants, they did their weight training in their homes or in a community gym facility except for the first six weekly sessions and monthly check-in sessions which were completed at the intervention site closest to the participant's home [31].

For the exercise intervention, all fitness professionals were trained in motivational interviewing and used the six supervised sessions at the beginning of the intervention to establish the participants' motivations and expectations for participation. This information was used to enhance adherence to the exercise intervention if necessary. Confidence to complete upcoming exercise sessions was assessed during all in person and phone counseling sessions, and appropriate discussion regarding what would increase confidence and reminders of what they did when they were successful were used, as per standard motivational interviewing techniques [40]. Participants in the exercise groups completed exercise logs. During weeks 1–6, fitness professionals collected and reviewed these logs during the group-based sessions. Weeks 7–52, exercise logs were collected and reviewed during the monthly group-based sessions. If participants missed one of these sessions, the fitness professionals called the participants. In addition during weeks 7–52 there were weekly calls for motivation and support for the first 6 months, then monthly for the remainder of that period. These brief phone calls were positive, encouraging, empathetic and non-confrontational. As with our prior studies, these calls were generally brief, rarely lasting longer than 15 min. Participants randomized to this group were referred to the American Cancer Society website if they had diet-related questions.

2.4. Weight-loss intervention

The weight-loss intervention was based on several earlier trials [41,42] and was tailored to the needs of breast cancer survivors [43,44], see Table 2 for an overview of the weight-loss intervention. The intervention started with a 24 week intensive phase that included weekly 1 h group meetings and provision of meals and snacks from a commercial manufacturer (NutriSystem®, Inc., Fort Washington, PA). The in-person meetings included a weigh-in, discussion of adherence to the planned dietary approach, and a behavioral modification lesson. The dietary approach included four NutriSystem® meals per day (breakfast, lunch, dinner, dessert), one protein shake per day, four servings of vegetables, three servings of fruit, two servings of low-fat dairy or lean protein such as fish or meat, and one serving of

fat, such as butter/spreads/oils/nuts/salad dressing/seeds. During the 24 week intensive phase, participants paid $105 each month for the NutriSystem® meals (75% discount compared with commercial costs of the meals); scholarships were provided to women who expressed concern about paying. Each in-person session included a behavioral modification lesson on topics such as goal setting, problem solving, preparing and practicing for difficult situations (e.g. holiday parties) etc. During each in-person session a different topic was addressed. Table 2 displays the specific topics that were covered. During the first 20 weeks, daily caloric intake was restricted to 1200–1500 kcals/day, representing a reduction of 40–50% from usual caloric intake. During weeks 20–24, participants were instructed to gradually incorporate "conventional foods" available in their grocery stores with a goal of staying at the same number of calories per day until reaching the study defined goal of 10% weight-loss. After week 24, there was a gradual increase in caloric intake of no > 500 kcal/day, which resulted in caloric intake between 1700 and 2000 kcal/day. From week 24 onwards, the aim was maintenance of a stable body weight throughout the remainder of the intervention. In this period, participants took part in monthly group meetings and had weekly phone contact with the dietitian. Groups of 2–6 participants were led by registered dietitians experienced with the NutriSystem® program. Group meetings took place in the community gym facilities where the exercise interventions also took place. Throughout the intervention, participants used paper or electronic food diaries to self-monitor their dietary intake. Dietitians reviewed these diaries either in-person or over the phone.

2.5. Exercise and weight-loss intervention

Participants randomized to this group received both the exercise intervention and the weight-loss intervention. These participants started with the group-based weight training sessions during the first six weeks. After these six weeks they continued this routine at home or at a gym as described above and additionally began with the weight-loss program.

2.6. Control group

Participants randomized to the control group were referred to the American Cancer Society website if they had diet-related questions. In addition, they were referred to their physician to discuss which types of exercise would be safe for them. The study staff instructed the participants to continue whatever exercise program they had been undertaking prior to enrollment in the study, but not to increase exercise, begin weight training, or engage in a supervised weight-loss program over the period of study participation.

Throughout the trial, the following strategies were in place to reduce the possibility that these factors would introduce bias affecting the findings of the trial. These included strategies to limit heterogeneity in the study population regarding basic knowledge of lymphedema, access to compression garments, and access to lymphedema treatment by a certified lymphatic therapist as needed. All participants, including the control group, attended a lymphedema education session prior to the start of any study related activities to provide information on how best to manage their lymphedema. This one-hour lecture was developed for the Physical Activity and Lymphedema trial [33]. The content included anatomy and function of the lymphatic system, as well as review of the National Lymphedema Network guidelines for lymphedema risk reduction, diagnosis and treatment,

self-care, exercise, and air travel [45]. In addition, all study participants were fitted for and provided with two free custom fitted lymphedema compression garments (arm sleeve, glove, or gauntlet) (BSN Medical, Charlotte, NC). Finally, all study participants were given access to certified lymphatic therapists for evaluation and treatment of lymphedema flares. Women who noted a change in symptoms lasting a week or longer were referred to certified lymphatic therapists for evaluation. If the therapist deemed treatment was needed, it was provided, free of charge, for as many sessions as clinically indicated.

2.7. Intervention adherence

Adherence to the intervention was assessed in several ways. Adherence to the dietary intervention was recorded by attendance at the in-person sessions. Adherence to the weight training and to the aerobic exercise was by self-report on the logs provided to participants by the exercise professionals.

2.8. Consent/IRB/DSMB

Approval was obtained from the IRB of the University of Pennsylvania. Written informed consent was obtained from all participants prior to enrollment. A Data Safety Monitoring Board was assembled to monitor unexpected adverse effects of the experimental intervention and, if needed, to implement safeguards to decrease or eliminate future risks. The DSMB included a biostatistician, an obesity intervention expert, a rehabilitation physician with expertise in oncology rehabilitation, and an exercise scientist. The group met quarterly by phone.

2.9. Outcomes

In person measurements took place at the University of Pennsylvania. All staff members who were involved in taking measurements were blinded to the group assignment of the participants. Participants were instructed not to reveal their group assignment to the study staff. An overview of all measurements over time is presented in Fig. 2.

2.9.1. Primary outcome: lymphedema—The primary outcome of the study is change in interlimb volume difference from baseline to 12 months. Additionally, we assessed several other lymphedema related outcomes, to be able to understand potential complexities of the effects of the intervention on lymphedema outcomes. Many measures of lymphedema are affected by factors that generally affect limb swelling, including ambient temperature, recent physical activity, humidity, barometric pressure, hydration status, alcohol intake, caffeine intake, and time of day [20]. These factors were documented for each patient and each measurement.

For the primary outcome, it was hypothesized that reductions in interlimb volume differences would be largest in the weight loss and exercise group, smaller in the weight-loss group, smaller in the exercise group, and smallest in the control group. Interlimb volume difference was assessed using perometry. The Optoelectronic Perometer (Juzo USA, Cuyahoga Falls, OH) was used to assess limb dimension and volume [46–48]. The device uses infrared light beams to scan the limb length and circumference; from these measurements volume and percent differences between arms is calculated. For all

participants, the compression garment was removed at least one hour before perometer measurement. The protocol included assessment of the arm length at which we would halt the measurement of arm volume, specific arm and hand positioning (fisted hand), and use of a motorized table on which the perometer was positioned so that the table could be raised and lowered to ensure that the extended arm to be measured was parallel to the floor. Test re-test evaluation of our perometer measurements indicated excellent reliability, with intra-observer correlation of 94% and inter-observer correlation of 98%.

As additional lymphedema related outcomes, we assessed the occurrence of therapist-delivered lymphedema flare treatment, cellulitic infections, a standardized clinical evaluation, and self-reported symptoms and pain.

2.9.2. Flare and cellulitic infections—Participants who reported a change in flare symptoms lasting one week or longer, regardless of group assignment, were evaluated by a certified lymphedema therapist. Flare evaluation was standardized and included changes in swelling by perometry, symptoms, and tissue tone and texture. In addition, the area of pain was documented along with the sensation (throbbing, aching, dull), duration and frequency of flares. Participants who reported a change in systemic symptoms consistent with possible cellulitic infections were referred to a designated physician within 72 h of onset of symptoms for evaluation.

2.9.3. Standardized clinical evaluation—All participants had a clinical evaluation at baseline and at 12 months with a certified lymphedema therapist. This therapist reviewed symptoms and the arm volume results measured by research staff prior to this appointment; assessed tissue tone and texture, symmetry between affected and unaffected sides, anatomic architecture (ability to see normal skinfolds, bones, joints); and conducted a neck and shoulder orthopedic screen. The therapist rated the extent of lymphedema according to the Common Toxicity Criteria version 3.0 [21].

2.9.4. Self-report of lymphedema symptoms—Symptoms were assessed using the Norman lymphedema questionnaire [49]. This survey has previously been shown to have a specificity of 0.90 and sensitivity between 0.86 and 0.92 to detect at least moderate lymphedema. In addition, we used the same lymphedema self-care log as used in earlier trials [32] to monitor possible factors that may have let to lymphedema onset. These factors were scored at baseline, 6 months and 12 months, and when participants were evaluated for possible flare.

2.9.5. Pain—Pain was rated using the Brief Pain Inventory [50], a reliable and valid instrument to assess pain across cultures and languages. In addition, the Penn Shoulder Score was used to assess participants' self-reported levels of pain, satisfaction and function of the shoulder [51]. This score was found to be reliable test-retest intra-class correlation: 0.94 and internally consistent (Cronbach alpha of 0.93).

2.9.6. Secondary outcomes: biomarkers of recurrence—To assess changes in biomarkers in the WISER Survivor trial, blood was drawn from all participants at baseline and 12 months, after a 12 h fast, in the morning. Participants were asked to drink an eight

ounce glass of water prior to the blood draw. Plasma and serum samples were prepared, aliquoted and stored at −80 °C until further analysis. In addition, PaxRNA and PaxDNA tubes were collected, for later evaluation of both RNA and DNA based changes.

The trial was designed to study effects of the intervention on biomarkers of mechanistic pathways hypothesized to link energy balance with recurrence risk. The pathways we focused on were based on research on mechanistic pathways in primary breast cancer [52–64], because of the lack of studies in breast cancer recurrence. The following pathways were identified as potentially relevant: insulin resistance & growth factors, sex steroid hormones, pathogenic angiogenesis, and inflammation/oxidative stress. As shown in Fig. 1, the WISER Survivor trial was interwoven with a pre-clinical animal study that assessed the effects of the same interventions (exercise, weight-loss, exercise and weight-loss, or no intervention) on breast cancer recurrence.

In the animal model, mammary tumors were induced in overweight mice by the doxycycline-dependent activation of HER2, an oncogene relevant to human breast cancer [65]. Withdrawal of doxycycline results in tumor regression and in cohorts of mice bearing dormant residual tumor cells, which eventually spontaneously relapse by mechanisms relevant to human breast cancer [66–69]. Overweight mice bearing residual disease were randomly assigned to exercise (aerobic exercise on a treadmill), calorie restriction, both of these interventions, or neither and followed for cancer recurrence. Biomarkers will be evaluated to explore the hypothesized relationship between energy balance and recurrence. To our knowledge, this is the first study to explore the impact of exercise and calorie restriction on cancer recurrence in an animal model. The animal model will guide additional mechanistic biomarkers to be tested in the WISER Survivor trial.

2.9.7. Secondary outcomes: health-related quality of life and psychosocial measures—The trial was designed to study quality of life outcomes, focusing on a lymphedema-related quality of life measures and body image. Quality of life was assessed at baseline, 6 months, and 12 months. Participants were asked to complete several surveys that covered different aspects of health-related quality of life.

2.9.8. Short-form health survey (SF-36) [70–72]—This survey is a widely used health survey which has been used extensively in breast cancer survivors [73–79]. It includes 36 items covering eight health domains: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions.

2.9.9. Quality of life scale for upper limb lymphedema (ULL-27) [80]—The instrument contains 27 items, divided into three dimensions (physical, psychological, and social quality of life), and is precise, sensitive and accurate on these dimensions [80].

2.9.10. Body image and relationships survey (BIRS) [81,82]—This survey has 32 items measuring attitudes about appearance, health, physical strength, sexuality, relationships, and social functioning. It has satisfactory test-retest reliability ranging from Spearman $\rho = 0.41$ to 0.80, and internal consistency [81].

2.9.11. Fatigue symptom inventory (FSI) [83,84]—This inventory assesses 14-items related to the severity, frequency, and daily pattern of fatigue as well as its perceived interference with quality of life, and is a valid and reliable measure of fatigue in cancer patients [83]

2.9.12. Work productivity—We used the validated work productivity and activity impairment questionnaire to assess these issues [85].

For the accompanying cost-effectiveness study (project 3 in Fig. 1), patients filled out the *EuroQol 5D* (*EQ-5D*[86,87]) at baseline, at 6 months and 12 months. The EuroQoL-5D is a validated instrument that provides a descriptive profile and index value that can be used in the clinical and economic evaluation of health care; it consists of questions in five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). In addition, the participants logged their health-care costs in cost diaries; details about this study will be reported elsewhere.

2.10. Additional physiologic measurements and surveys

2.10.1. Muscle strength—Strength of the arms and legs was tested with standardized bench press and leg press equipment at baseline and after 12 months, using the same protocol as used in earlier trials [9]. The maximum amount of weight that was lifted once (1 Repetition Maximum = 1 RM) was assessed for the bench press and the leg press. Changes in strength were assessed to study whether physical function improved in the intervention groups compared to the control group.

2.10.2. Maximal aerobic fitness—Maximal aerobic fitness was assessed at baseline and after 12 months; heart rate during this test was measured by 12-lead ECG monitoring. The test started with a 5 min rest after which blood pressure, resting heart rate and ECG were measured. Then the participant started with two warmup stages, each lasting 3 min. The first was at 1.7 mph and a 0% grade, and the second was at 1.7 mph and a 5% grade followed by a gradual increase in intensity as specified by the Modified Bruce protocol [74,75] every 3 min until exhaustion. During the last minute of every 3 minute interval, blood pressure, heart rate and ECG were measured.

2.10.3. Height, weight and body composition—Body weight was measured on a calibrated scale at baseline, 6 months and 12 months. Height was assessed at baseline only. Fat mass, fat free mass, bone density were measured by dual energy x-ray absorptiometry (DXA); from those measurements visceral adipose tissue areas and subcutaneous adipose tissue areas were estimated using dedicated software (Hologic, Inc., Bedford, MA) at baseline and after 12 months.

2.10.4. Diet—The Dietary History Questionnaire (DHQ-II) [88] was used to assess usual dietary intake; validation studies indicate that this questionnaire is better in estimating absolute intakes than the Block and Willett food frequency questionnaire [89]. The DHQ-II was administered at baseline and 12 months.

2.10.5. Physical activity—The Modifiable Physical Activity Questionnaire [90] was used to assess physical activity levels. This questionnaire asks about physical activity over the past year in three domains: leisure-time, occupational, and sedentary. Validity of the leisure activity section of the questionnaire was demonstrated through comparisons with the accelerometry (rho = 0.62). It was assessed at baseline and 12 months.

2.10.6. Demographics and other personal factors—Self-report surveys on demographics and other personal factors were developed and used in earlier trials by our group [33,34]. A general survey with questions on marital status, race, income, educational level and occupational status was administered to participants at baseline. Interview-administered surveys on medical history, cancer stage and treatment, medication use and menstrual tracking were taken at baseline and were repeated at twelve months. Additionally, at twelve months, all participants completed an injury history survey to log any major physical or mental health events they experienced over the past year.

2.10.7. Statistical considerations—The study was designed to have 80% power to detect differences in interlimb volume difference −2.62% −5.24% and −7.86% in the exercise, weight-loss, and combined exercise and weight-loss groups, respectively, compared to the control group. Using a Type I error of 0.05 and a Holm-Bonferroni adjustment for multiple comparisons, 79 participants per group were needed. We anticipated a 10% attrition rate based on our earlier trials, and planned to enroll n = 88 participants per group adding up to a total number of 352 participants in the trial. The trial was designed as a four group intervention, and not as a standard 2 × 2 factorial design, because 2 × 2 designs assume a lack of interaction between the two interventions and combine samples to assess the effect of each factor. We wished to allow for the possibility of interaction and therefore designed the study with sufficient power to consider each arm individually.

All primary analyses will be conducted using the intention-to-treat principle, including each participant in the group to which she was randomized regardless of adherence to the assigned strategy. We will use mixed models to test whether changes in interlimb volume difference differ between groups.

3. Results and discussion

During a period of 39 months, we randomized 351 patients into the WISER Survivor trial. The average age of women enrolled in the trial was 59.4 years, and their BMI was 34.0 kg/m^2; baseline characteristics, presented in Table 3 were similar between groups. We were successful in recruiting a diverse population: 35% of participants were Black women. The interlimb volume difference was similar for all groups at baseline.

Thirteen participants were diagnosed with a cancer recurrence during the trial, and 58 participants dropped out of the study (Table 4). We collected 12 month post-intervention data of 280 participants. Out of the 338 participants without a breast cancer recurrence, 83% completed the trial and participated in the post-intervention measurement. Baseline characteristics of the n = 280 participants with post-intervention data were very similar to the characteristics of the total group of 351 participants that started the trial, with an average

age of 59.7 (SD 8.6 years), 63% White women, 34% Black women, and 3% other race, and an interlimb volume difference at baseline of 8.9% (SD 15.1).

The primary goal of WISER Survivor is to test the combined effect of exercise and weight-loss on changes in lymphedema. An important strength of the trial is our assessment of a range of lymphedema related outcomes, enabling examination of the effect of the intervention on all aspects of lymphedema. We hypothesize that the combined effects of exercise and weight-loss on lymphedema outcomes will be larger than the separate effects for the following reasons. Weight-loss through caloric restriction may reduce arm swelling by using the fuel in the excess peripheral fatty tissue networks prevalent in affected arms. In addition, compression garments may work better as the subcutaneous fat depots shrink. Moreover, as obesity is considered a state of inflammation, weight-loss may reduce the inflammatory state of the lymphatic system which may translate into improved lymphedema outcomes.

Successful recruitment of 351 breast cancer survivors required active as well as passive recruitment approaches. The exercise intervention used was adapted from a prior study that required women to attend in person sessions at a community gym for a full year [33]. In that prior study, exercise adherence was 79% [15]. Feedback from participants in the prior study and other research by our team [37] led our research team to pilot test a home based adaptation of the intervention. High adherence to this new home adaptation in the pilot (unpublished results) led to the decision to make the WISER Survivor trial exercise intervention largely home based.

The interlimb volume difference at baseline was 8–10%. This was slightly lower than the 15–17% as observed in our earlier trial [15]. In our previous trials, we used slightly different eligible criteria, requiring an interlimb difference of at least 10% or a clinically confirmed diagnosis of lymphedema. For WISER Survivor, we additionally recruited women who were not previously aware that they had lymphedema but whom we identified using a valid, reliable, self-reported survey [49]. If they responded positively to any of the questions on that survey, they were screened for lymphedema by a certified therapist, and if confirmed they were eligible for the trial.

The WISER Survivor trial has several unique features. The first is the use of a commercially available product (NutriSystem®) during the first 24 weeks of the lifestyle modification for weight-loss. Earlier trials primarily used diet and/or physical activity and/or behavioral modification to achieve weight-loss [79].

A second unique feature of the WISER Survivor trial is its conduct within the broader scope of transdisciplinary research as depicted in Fig. 1. This enables the comparison of biomarkers for recurrence in both mice and humans. The pre-clinical study aids in prioritizing which biomarkers will be tested in the WISER Survivor trial by their likelihood of playing a mechanistic role; ideally, it will observe effects of the energy balance interventions on recurrence and changes in biomarkers that will point to specific mechanistic pathways through which this effect works. Using data from WISER Survivor, we will then assess whether similar interventions in women have similar effects on the same biomarkers.

The WISER Survivor trial collected a wealth of data to study potential effects of the interventions on lymphedema outcomes, biomarkers of recurrence, quality of life, and other physiological and functional outcomes. In addition, interrelationships among outcomes can be studied and characterized.

Acknowledgments

State Cancer Registry Representatives: Robin Otto (PA Cancer Registry contact), James Rubertone (PA Cancer Registry Contact), Dr. Lisa Paddock (NJ Cancer Registry), Jie Li (NJ Cancer Registry). Penn Cancer Network staff: Cathy Belt, Cindy Stern. Hospital Partners: Caitlin Beaudoin (Doylestown Hospital), Dr. Beth Dupree (Holy Redeemer Hospital), Dr. Tapan Kikani (Holy Redeemer Hospital), Heidi Volpe (Holy Redeemer Hospital), Cindy Brockway (Chester County Hospital), Sara Hollstein (Paoli Hospital), Margaret Beauchesne (Phoenixville Hospital), Dr. Lawrence Solin (Einstein Medical Center), Jeff Mealey (Einstein Medical Center), Susan Van Loon (Virtua Health System), Dr. Crystal Denlinger (Fox Chase Cancer Center), Louise Baca (Kennedy Cancer Center), Karen Swenson (Kennedy Cancer Center), Jennifer Torres, (St. Mary Medical Center), Dr. Stacy Krisher (St. Mary Medical Center). Fitness Facility Partners: Roger Schwab (Main Line Health and Fitness), Rhonda Hamilton (Upper Main Line YMCA), Lionville YMCA, Joe Fuhrman and Jill Makkay (Hamilton YMCA). NutriSystem®: Mandi Knowles, RDN, LDN and Courtney M McCormick, MPH, RDN, LDN.

Funding

This work was funded by National Cancer Institute grant U54CA155850 (Kathryn Schmitz).

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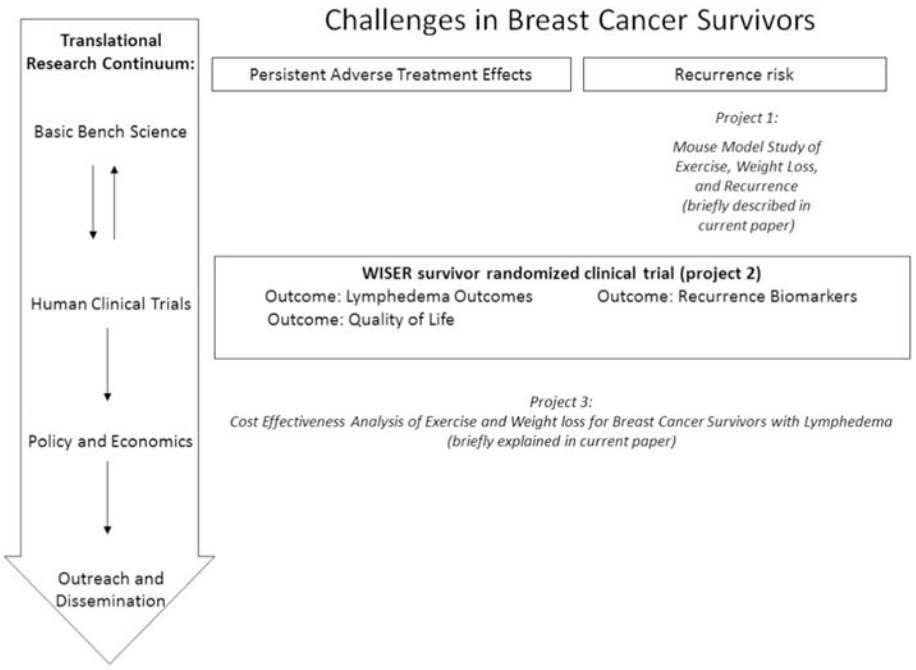

Fig. 1.

Overview of three interwoven projects conducted at the Penn TREC center of which the WISER Survivor trial was part. Project 1 was an animal model of breast cancer recurrence. Project 2 was the WISER Survivor trial. Project 3 was a cost-effectiveness analysis of the WISER Survivor trial.

	Baseline	6 months	12 months
Lymphedema outcomes - Perometry - Clinical evaluation (not at 6 months) - Norman survey - Lymphedema self-care log - Brief Pain Inventory - Penn Shoulder Score	X	X	X
Blood draw	X		X
Quality of Life - Short-Form Health Survey (SF-36) - Specific Quality of Life Scale for Upper Limb Lymphedema (ULL- 27) - Body Image and Relationships Survey (BIRS) - Fatigue Symptom Inventory (FSI) - Work productivity and activity impairment	X	X	X
Muscle strength & fitness	X		X
Dexa scan	X		X
Diet, physical activity, medical history and demographics	X		X
Cost-effectiveness - EuroQoL-5D - Cost diaries	X	X	X
On an 'as needed' basis continuously during the trial	*Adverse events & flare-ups*		

Fig. 2.

Timeline explaining assessment of various outcomes, surveys and tests in the WISER Survivor trial.

Table 1

Overview of the dosage of exercise prescribed by intervention week for participants in the exercise or exercise and weight-loss arms of the WISER Survivor trial.

Week	Supervision	Weight training sessions per week	Weight training sets/exercise	Weight training time per session	Aerobic sessions per week	Aerobic time per session	Total exercise time/week
1–3	One supervised, one unsupervised weight training session per week	2	2 sets of 10 reps/exercise	70–90 min	3	30 min	230–270
2–4		2	2 sets of 10 reps/exercise	70–90 min	4	30 min	260–300
5–6		2	3 sets of 10 reps/exercise	70–90 min	5	30 min	290–330
7–52	Weekly calls for motivation & support for first 6 months, then monthly for months 6–12. Monthly group meetings for ongoing behavioral support group weight training	2	3 sets of 10 reps/exercise	60–80 min	6	30 min	300–340

Contemp Clin Trials. Author manuscript; available in PMC 2018 February 19.

Table 2

Overview of the weight-loss intervention by intervention week for participants in the weight-loss or exercise and weight-loss arms of the WISER Survivor trial Lymphedema Care for Participants.

Week	Supervision	Frequency of sessions	Meeting length	NutriSystem® meal replacements provided	Caloric intake
1–19	Weekly meetings/lessons[a] led by registered dietitian	1 per week	60 min	4 daily meals: breakfast, lunch, dinner, dessert	1200–1500 kcal/day
20–24	Weekly meetings/lessons[b] led by registered dietitian	1 per week	60 min	Gradually decreasing from 3 in week 20 to none in week 24, gradually increasing conventional foods	1200–1500 kcal/day
Remainder of weeks	Monthly meetings/lessons[c] led by registered dietitian, weekly phone calls or emails from registered dietitian between meetings	1 per month	60 min	None	Gradually increasing to 1700–2000 kcal/day

[a]Lessons discussed the following topics 1: Introduction to the program, 2: External cues, 3: Overweight as a risk factor, 4: Problem Solving, 5: Fruits and Vegetables, 6: Stress and Emotional Eating, 7: Dealing with Negative Thoughts, 8: Dealing with Lapse and Relapse, 9: Social Support, 10: Healthy Dining Out, 11: Alcohol, 12: Handling Holidays/Vacations, 13: Coping with Cravings, 14: Calcium and Vitamin D, 15: Continuum of Cancer Care, 16: Body Image, 17: Mood, Hunger, and Overeating, 18: Dietary Fat, 19: Fad Diets.

[b]Lessons discussed the following: 20: Conventional Foods/Tipping the Calorie Balance, 21: Ways to Eat Fewer Calories, 22: Grocery Shopping, 23: Healthy Eating, 24: Ingredients and Recipes.

[c]Lessons discussed the following: 25: Volumetrics/Caloric Density, 26: Tune Up, 27: Ways to Stay Motivated, 28: Maintaining Energy Balance, 29: Becoming a Weight Loss Expert, 30: Preventing a Weight Relapse.

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Table 3

Baseline characteristics of participants in the four arms of the WISER Survivor trial

	Control group n = 90	Exercise n = 87	Weight-loss n = 87	Exercise and weight-loss n = 87
Personal characteristics				
Age in years (mean + SD)	59.0 (8.5)	59.1 (8.1)	59.4 (9.2)	60.0 (9.0)
BMI in kg/m^2 (mean + SD)	34.0 (5.7)	34.0 (6.2)	33.8 (5.6)	34.2 (6.3)
Race White n (%)	66 (73%)	50 (57%)	52 (60%)	50 (57%)
Black	22 (24%)	36 (41%)	32 (37%)	32 (37%)
Other	2 (2%)	1 (1%)	3 (3%)	5 (6%)
Educational status high school or less n (%)	19 (21%)	15 (17%)	12 (14%)	18 (21%)
Some college	28 (31%)	29 (33%)	36 (41%)	29 (33%)
College Grad or more	43 (48%)	43 (49%)	39 (45%)	40 (46%)
Lifestyle				
Energy intake at baseline in kcal/day (mean + SD)	1787 (957)	1689 (809)	1727 (1135)	1665 (946)
Physical activity level at baseline in MET-hr./week (median [IQR])	5.0 [2.3, 10.3]	4.0 [1.4, 10.0]	5.4 [1.5, 14.5]	2.9 [0.5, 11.3]
Clinical characteristics				
Time since diagnosis in years, mean + SD	8.1 (5.1)	7.7 (5.4)	7.5 (5.6)	7.3 (5.1)
Cancer stage at diagnosis[a] 0 n (%)	10 (11%)	6 (7%)	5 (6%)	3 (3%)
I	18 (20%)	23 (26%)	17 (20%)	14 (16%)
II	22 (24%)	23 (26%)	28 (32%)	28 (32%)
III	16 (18%)	10 (11%)	18 (21%)	19 (22%)
Unknown	24 (27%)	25 (29%)	19 (22%)	23 (26%)
Number of lymph nodes removed (mean + SD)	12.3 (9.3)	12.7 (9.4)	12.5 (9.9)	12.0 (8.3)
Radiation therapy n (% yes)	73 (81%)	73 (84%)	69 (79%)	73 (84%)
Chemotherapy n (% yes)	74 (82%)	65 (75%)	71 (82%)	79 (91%)
Currently on tamoxifen or aromatase inhibitors n (% yes)	41 (46%)	35 (40%)	32 (37%)	30 (34%)
Breast cancer-related lymphedema characteristics				
Interlimb volume difference in percentage (mean + SD)	+9.6 (14.4)	+8.8 (16.6)	+8.8 (13.5)	+7.6 (13.7)
Self-report of lymphedema (Norman survey [49])				
Overall score for extremity	3.38 (2.72)	3.47 (2.65)	3.23 (2.71)	3.22 (2.71)
Overall score for breast/torso	0.94 (0.88)	1.10 (1.01)	0.84 (0.90)	0.97 (0.95)
# of symptoms reported (range 0–14)[b]	5.50 (2.81)	5.74 (2.71)	5.18 (2.76)	5.03 (2.81)
Symptom severity (range 0–4)[2]	1.92 (0.71)	1.96 (0.81)	1.81 (0.74)	1.84 (0.79)

[a] Based on self-report.

[b] Possible values were zero (did not have symptom) to four (very severe) for each symptom; there were 14 possible symptoms (rings too tight, watch too tight, bracelets too tight, clothing too tight, puffiness, couldn't see knuckles, couldn't see veins, skin felt leathery, arm felt tired, pain, pitting, swelling after exercise, difficulty writing, or 'other').

Table 4

Description of the number of participants randomized to WISER Survivor and retention over time.

	Total	Control	Exercise	Weight-loss	Exercise and weight-loss
At baseline	351	90	87	87	87
Drop-outs during the trial	58	19	13	18	8
Recurrences during the trial	13	3	3	1	6
Number for analysis at 12 months	280	68	71	68	73
Percentage of participants without recurrence who completed the trial	83%	78%	85%	79%	90%

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