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Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors: a randomized, controlled trial

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Abstract

Targeted exercise training could reduce risk factors for fracture and obesity-related diseases that increase from breast cancer treatment, but has not been sufficiently tested. We hypothesized that progressive, moderate-intensity resistance + impact training would increase or maintain hip and spine bone mass, lean mass and fat mass and reduce bone turnover compared to controls who participated in a low-intensity, non-weight bearing stretching program. We conducted a randomized, controlled trial in 106 women with early stage breast cancer who were >1 year post-radiation and/or chemotherapy, ≥ 50 years of age at diagnosis and postmenopausal, free from osteoporosis and medications for bone loss, resistance and impact exercise naïve, and cleared to exercise by a physician. Women were randomly assigned to participate in 1 year of thrice-weekly progressive, moderate-intensity resistance + impact (jump) exercise or in a similar frequency and length control program of progressive, low-intensity stretching. Primary endpoints were bone mineral density (BMD; g/cm²) of the hip and spine and whole body bone-free lean and fat mass (kg) determined by DXA and biomarkers of bone turnover—serum osteocalcin (ng/ml) and urinary deoxypyridinoline cross-links (nmol/mmolCr). Women in the resistance + impact training

program preserved BMD at the lumbar spine (0.47 vs. -2.13%; $P = 0.001$) compared to controls. The resistance + impact group had a smaller increase in osteocalcin (7.0 vs. 27%, $P = 0.03$) and a larger decrease in deoxypyridinoline (-49.9 vs. -32.6%, $P = 0.06$) than controls. Increases in lean mass from resistance + impact training were greatest among women currently taking aromatase inhibitors compared to controls not on this therapy ($P = 0.01$). Our combined program of resistance + impact exercise reduced risk factors for fracture among postmenopausal breast cancer survivors (BCS) and may be particularly relevant for BCS on aromatase inhibitors (AIs) because of the additional benefit of exercise on muscle mass that could reduce falls.

Keywords

Osteoporosis; Resistance exercise; Body composition; Neoplasms; Aromatase inhibitors

Introduction

There are approximately 2.5 million breast cancer survivors (BCS) in the U.S. [1]. Compared to their cancer-free peers, BCS are at higher risk of fracture [2, 3]. Prior to their cancer diagnosis and treatment, BCS are no more likely to fracture than other women; however, systemic treatment increases fracture risk [4]. Chemotherapy, chemotherapy-induced menopause, and aromatase inhibitor (AI) treatment accelerate bone loss and bone turnover [5–10]. In addition, inactivity related to cancer treatment can weaken the skeleton [11, 12] cause muscle loss and lead to fat gain [13–16]. These changes in body composition place BCS at higher risk of obesity-related disease [17] breast cancer recurrence [18], frailty [19], and fractures [4]. There is no pharmacologic strategy to concomitantly improve all three components of body composition affected by breast cancer treatment. Further, current clinical guidelines do not endorse routine use of bisphosphonates for BCS with low bone mass (e.g., osteopenia), but rather recommend lifestyle advice to prevent bone further bone loss [20].

Exercise improves all three components of body composition in women without a cancer diagnosis; but it is not clear if exercise has the same effects in BCS [21, 22]. A combination of resistance plus impact training is specifically suited to reverse or slow age-related declines in bone and muscle mass and can also reduce body fat [23–26] but, the combined intervention has not been evaluated in BCS [22]. We conducted a randomized controlled trial in postmenopausal BCS comparing a 12-month resistance + impact exercise training program to a 12-month control condition of flexibility (stretching) sessions. We hypothesized that moderate-intensity resistance + impact exercise would increase muscle and bone mass, reduce fat mass, and lower bone turnover compared to flexibility exercise that places little stress on the musculoskeletal and metabolic systems. Our study targeted non-osteoporotic women who were at increased risk for bone loss due to age and cancer treatment [20] and for whom few evidence-based, non-pharmacologic strategies currently exist [27].

Methods

Design

We conducted a 12-month single-blind randomized controlled trial comparing two parallel groups receiving progressive, supervised exercise: (1) moderate-intensity resistance + impact training (experimental) and (2) flexibility training (control). Primary outcomes were measured at baseline, 6 and 12 months. All testing and exercise training took place at Oregon Health & Science University (OHSU) between October 2006 and January 2009. The study was approved by the OHSU Institutional Review Board.

Participants

Women were recruited through the Oregon State Cancer Registry, clinician referral, community events, study advertisements, and information sessions. Interested women were screened to determine if they met the following eligibility criteria: diagnosis of stage 0–3a breast cancer at or after age 50, postmenopausal, ≥ 1 year post-chemotherapy or radiotherapy, non-osteoporotic, no bone altering medication other than adjuvant hormone therapy, physician clearance to exercise and, no regular participation in resistance and/or impact exercise (less than two 30-min sessions per week) in the past month, physical and cognitive ability to complete study testing.

The PASS 2000 program [28] was used to conduct the power analysis based on a 2×3 mixed-design analysis of variance using initial and change values for primary outcome measures from our prior work [29]. At $n = 35$ per group, we had power of 0.81 to 0.99 to detect a significant group by time interaction for bone, lean and fat mass measures at $\alpha < 0.01$. To protect against 20% attrition [29, 30] we planned to randomize at least 44 participants per group.

Study interventions

Participants in both groups were prescribed an exercise program consisting of two supervised classes and one home-based session per week for 12 months. Each exercise session lasted 45–60 min. Certified exercise instructors were trained and supervised by the research team to deliver the exercise protocols. Session completion was tracked in training logs for both class and home programs. Home programs began after 1 month of supervised classes to provide time to learn proper form and safety before exercising at home. Women followed a written manual that outlined each week's exercise program.

The resistance plus impact intervention (*POWIR*: Prevent Osteoporosis With Impact + Resistance) used in this study was based on our prior interventions in women without cancer [31, 32]. *POWIR* complied with the American College of Sports Medicine (ACSM) recommendations for preserving bone health in postmenopausal women by using resistance and/or impact exercise at moderate to high bone loading forces [23, 33] and with ACSM recommendations for resistance training at loads corresponding to 60–70% of 1-RM for 1–3 sets of 8–12 repetitions to build lean mass and strength in novice weightlifters and older adults [34, 35]. Free weights were used to apply resistance—dumbbells for upper body, weighted vests for lower body, and a barbell for one combined upper + lower body exercise. Initial intensity and progression were based on our previous studies [31] (Table 1). Selected exercises utilized musculature with attachments directly on the skeletal sites of interest [31, 36] and included wall-sits, 90° squats, bent-knee dead lifts, forward lunges, lateral lunges, 1-arm row, chest press, lateral raise, and push-ups. Impact exercise consisted of two-footed jumps from the ground to a target height 1" from the floor with a bent-knee landing, performed with weighted vests on and in sets of 10. During a single exercise session participants warmed up, performed 1–6 jump sets, 1–2 sets of 3–4 upper body, and 3–4 lower body exercises, then cooled down. At home the same exercises that were performed in class were done except the deadlift, resistance bands replaced free weights for upper-body exercises, and lower body exercises were performed without weighted vests because of the inconvenience of transporting them. Training volume progressively increased by increasing band thickness, squat and lunge depth, and sets and repetitions.

Participants in the control group (*FLEX*) performed a series of whole body stretching and relaxation exercises in a seated or lying position. Selected exercises were chosen to minimize weight-bearing forces so that little stimulus to the musculoskeletal system was applied and energy expenditure was minimal.

Participant safety in training

Each woman had physician clearance to participate in either exercise program. Participants reported any training-related injury to the training team and in training logs. If necessary, adjustments in the training program were made on an individual basis and recorded. Any woman with serious or persistent symptoms was asked to refrain from exercise until her physician cleared her return to training. Women who were prescribed compression sleeves for lymphedema ($n = 5$) wore their sleeves during exercise training. To document any effect of the program on lymphedema we compared circumferences between arms measured at the base of the middle finger, wrist, and distal forearm at 0, 3, 6, and 12 months of training [37]. Women reported symptoms of lymphedema to the trainer and in training logs.

Measures

At baseline, written informed consent was obtained followed by completion of questionnaires, body composition testing, and blood/urine collection. Providing biological specimens was offered as an optional part of the study. Tests followed standard operating procedures, were administered by trained technicians blinded to group assignment, and were repeated at 6 and 12 months. Randomization was stratified by adjuvant hormone therapy use (AI or SERM vs. none) and current aerobic activity (≥ 90 vs. < 90 min/week). Group assignments were placed in sealed, sequentially numbered envelopes and opened by the participant following the completion of baseline testing.

Bone mineral density (g/cm^2) of the proximal femur (total hip, greater trochanter, femoral neck) and anterior-posterior lumbar spine ($\text{L}_1\text{--}\text{L}_4$), bone-free lean mass (kg), and fat mass (kg) were assessed by dual energy X-ray absorptiometry (DXA; Hologic QDR Discovery Wi; software version 12.0). DXA scans were performed by licensed technicians blinded to participant group and were analyzed by the same technician. Coefficients of variation for DXA measures in our laboratory are 1–1.5% [29].

Bone turnover was assessed by serum osteocalcin (ng/ml), a byproduct of bone formation and urinary deoxypyridinoline cross-links (nmol/l), a byproduct of bone degradation adjusted for urine volume (creatinine: mmol/l). Blood and urine samples were collected in the morning after 12-h fast and stored at -70°C for analysis. Analyses were conducted in batch by ELISA with commercial kits (Diagnostic Systems Laboratory, Inc). Inter-assay CVs from our laboratory are 5.7 and 6.2% and intra-assay CVs are 8 and 4.8% for deoxypyridinoline and osteocalcin, respectively.

Demographic and clinical history was obtained by self-report. Medication use was updated at 6 and 12-month visits. Chronic medical conditions were assessed by the Charlson Comorbidity Index [38]. Menopausal status of participants in each group was confirmed by $\text{FSH} > 30$ mIU/ml and estradiol < 20 pg/ml based on radioimmunoassay of baseline samples. To account for changes in physical activity and diet outside of the intervention that could affect primary outcomes, we measured habitual physical activity with the Community Health Activity Model Program for Seniors (CHAMPS) physical activity questionnaire for older adults [39] (kcal/day in all activities) and habitual calcium (dietary + supplemental) and total energy intake with the 2005 Block Food Frequency Questionnaire at each visit [40].

Statistical analysis

To characterize the sample, we computed means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Separate one-way ANOVAs were conducted to check the validity of randomization and identify covariates. To account for the potential influence of age, time since diagnosis, and adjuvant hormone

therapy on changes in outcome variables over time, these variables were included as covariates in all analyses. The intent-to-treat (ITT) analysis was performed using Hierarchical Linear Modeling (HLM; HLM 6.08 software) [41] analyzing each participant according to her originally assigned group and regardless of missing 6 or 12-month data. HLM is superior to other approaches to handling missing data, such as mean imputation or last observation carried forward [42, 43]. In addition to ITT analysis, data from participants with complete baseline and 12-month data were considered to evaluate intervention effects in participants who completed the study using separate 2 (group) $\times$ 3 (time) mixed-design analysis of covariance (MD-ANCOVA) for each outcome. To examine the influence of adjuvant hormone therapy use on the impact of the intervention on primary outcomes, HLM was repeated to examine effect modification. Significant interactions were graphed and interpreted to determine the nature of the effect moderation.

Results

In response to recruitment efforts 359 women showed interest in the study. Of these, 106 women enrolled in the trial and were randomized to POWIR ($n = 52$) or FLEX ($n = 54$). Eighty-eight participants consented for biological specimen collection. Participant flow is outlined in Fig. 1. Women who withdrew from the program did not differ from those who remained in the study on any baseline characteristic or outcome. Participants were older (>60 years), had high BMI, normal skeletal health (T score ≥ -1.0) and an additional chronic condition other than cancer (Table 2). Most women had stage I or II breast cancer and varied in their time since breast cancer diagnosis (SD = 3.1 years). Nearly all participants received radiation therapy, about 60% also received chemotherapy and about half were currently taking adjuvant hormone therapy—mostly AIs. Women consumed slightly less than the RDI for calcium, most likely related to their modest self-report caloric intake, and were active (Table 3). Intervention groups were not different at baseline. Energy intake and calcium intake did not change over time for either group and were not included as covariates in subsequent analyses (Table 3). Ten women changed their adjuvant hormone therapy regimen during the 1-year intervention, either discontinuing AIs ($n = 4$) or SERMs ($n = 4$) altogether or switching from a SERM to an AI ($n = 2$). The distribution of women changing therapy was equal between study groups. Removing these women from analyses did not alter statistical outcomes.

Total, supervised-only and home-only attendance averaged 57, 76, and 23% for POWIR and 62, 72, and 44% for FLEX groups. Attendance to home sessions was significantly better in FLEX than POWIR, $t(64) = 3.60$, $P < 0.01$. Final intensity for lower body resistance exercises was just shy of the planned progression, stopping at 13% of body weight in weighted vests and 10–12 RM for upper body exercises by month 9. There were no injuries or adverse events associated with participation in either intervention and no significant change in upper-extremity circumference measures over time (data not shown).

Using the ITT approach, there were significant differences over time between POWIR and FLEX groups for lumbar spine BMD (Coefficient on slope of time = 0.013, SE = 0.004, $t(99) = 3.64$, $P < 0.01$). Based on observed values from participants with complete data sets, BMD at the spine was preserved in the POWIR group compared to a 2% loss in controls (Table 3). There were no significant group differences over time at any hip site. Over time, BMD was maintained at both skeletal sites compared with consistent declines in BMD at each 6-month interval (Fig. 2). Changes in serum osteocalcin over time differed by group (Coefficient on slope of time = -1.07 , SE = 0.49, $t(83) = 2.17$, $P = 0.03$) and a trend was apparent for deoxypyridinoline (Coefficient on slope of time = -0.10 , SE = 0.05, $t(84) = 1.92$, $P = 0.06$). Osteocalcin increased in FLEX but remained steady in POWIR, while deoxypyridinoline cross-links decreased more in POWIR than FLEX (Table 3). In per

protocol analyses, significance was maintained for both lumbar spine BMD and osteocalcin (Table 3), with significant linear trends ($P < 0.01$).

Changes in whole body fat mass and % body fat did not differ between groups. Lean mass increased in the POWIR group to a greater extent among women currently taking AIs than POWIR participants not on AI treatment, whereas lean mass did not change appreciably among FLEX regardless of AI use (Coefficient of group by AI vector on slope of time = 922.50, SE = 367.98, $t(95) = -2.51$, $P = 0.01$ see Fig. 3). There was no effect modification of AI use on bone or fat measures or of SERM use on any primary outcome.

Discussion

In contrast to BCS who participated in stretching exercise and consistently lost BMD at the lumbar spine over 1 year, women who participated in a program of combined resistance + impact training (e.g., POWIR) maintained BMD at this site. In addition to BMD, the POWIR program caused more favorable changes in bone turnover, resembling that achieved by anti-resorptive therapy [44]. POWIR did not improve lean or fat mass; however, moderator analysis detected differences between groups that depended upon adjuvant hormone therapy use. That is, women who were in the POWIR group and on AIs had the greatest increase in lean mass, while women in the FLEX group who were not on AIs appeared to have a slight decrease in lean mass.

The efficacy of our resistance + impact exercise program to prevent declines in BMD at the spine is consistent with the results from our previous trial in premenopausal women without cancer [31]. We are the first to report that exercise can preserve bone mass at the lumbar spine, a clinically relevant fracture site in BCS, though we failed to achieve similar results at the hip. Programs at our achieved training volume have increased hip BMD in premenopausal women when performed 3–5 times per week [31, 45], but the postmenopausal hip may require a greater load to adapt [45]. Combined programs of impact plus resistance training better target the spine than the hip in postmenopausal women without cancer [36]. Studies with conservative jump training programs have not improved hip BMD in cancer-free older women [45, 46], whereas those employing atypical loading [47], more jumps or more intense resistance exercise were effective [48, 49]. The lower intensity of home exercises, lower adherence to the home program and modest jump number in our study may have contributed to an overall suboptimal stimulus at the hip. The hip may also simply require a longer time period to adapt to moderate-intensity training in older women. Snow et al. [32] reported that a similar exercise program to ours did not affect hip BMD after 9 months, but was later found to have preserved BMD at a 5-year follow-up in women continuing to exercise compared to losses among inactive women. Future studies should consider longer training programs, inclusion of exercises that load the hip in unusual patterns, greater jump number, increased frequency of supervised sessions and/or strategies to maintain training intensity at home.

The POWIR program did not favorably shift body composition; however, our results suggest that current AI use influences changes in body composition in response to resistance training. The ability of exercise of any type to improve body composition in BCS of any age is unclear since results from RCTs tend to be mixed [22]. Schmitz et al. [50] reported significant gains in lean body mass among recently treated BCS who strength trained for 6 months, but did not replicate these findings among BCS with or at risk for lymphedema, who also notably did not use AIs [51, 52]. In our study, we found greater between group differences in lean body mass over 1 year among AI users that suggest a potentiating influence of AIs on training-induced hypertrophy. Recently, AI use has been shown to increase free testosterone and lean mass in BCS without concomitant changes in % body fat

[53]. Kenney et al. [54] reported preservation of lean mass with a combination of dihydroepiandrosterone supplementation plus exercise in frail older women compared to losses in controls. A possible synergistic effect of AIs and resistance training on lean mass in BCS is an intriguing finding that is worth further study.

The strengths of our study are the translation of a targeted bone loading program shown effective in non-clinical populations to improve BMD in cancer survivors, our study of older BCS who are rarely the focus of exercise trials, and exclusion of bisphosphonate use to reduce confounding. Notable limitations of our study include a lack of a usual care control group, inclusion of aerobically active women, and modest attrition. Given the known benefits of physical activity we felt it would be unethical to assign women to a non-exercise control group. We selected an exercise type, e.g., stretching, that was the least likely to produce an osteogenic stimulus to bone and expend energy, but that could produce benefits for range of motion and well being. The 12-month changes in controls were minimal or followed age-expected trends and so we felt the flexibility program was appropriate. We did not exclude women who were aerobically active from participating because impact and resistance exercise load the skeleton in distinctly different ways than aerobic exercise and are superior for osteogenesis [36, 55]. However, aerobically active participants may have replaced their habitual activity with the intervention program causing no net change in energy expenditure or body fat (Table 3). Retention in the study was modest (62%) and this may have affected the ability of the program to shift lean and fat mass and bone mass at the hip, leaving us potentially underpowered for these variables. However, we fell only three participants short of the estimated sample size for the per protocol analysis, and we did not have any borderline *P* values where an inadequate sample size might bring into question whether or not we were underpowered to detect significance. Exercise studies that include a BMD outcome should ideally last a year or longer to allow for completion of bone remodeling cycles [27], but the tradeoff to longer programs is risk of attrition and waning adherence over time. Only three randomized, controlled trials with center-based training programs in BCS have lasted for 1 year and all reported lower attrition [51, 56, 57]; however, ours was the only study specific to older women and that required women to attend scheduled group exercise classes. Most women cited logistical issues for dropping out (Fig. 1), which we largely attribute to the constrained schedule, unusual class times, inconvenient parking and travel to the facility. Clearly, we need to better understand the conditions that will yield optimal adherence to resistance training in older in BCS to promote this program in clinical practice. Adherence among women who stayed in the program was comparable to the other center-based trials [51, 56, 57]. Even with drop out, retention in our study is better than that reported for bisphosphonate use with approximately 50% of patients who are prescribed this medication discontinuing use within 6–12 months [58].

Our program was able to preserve bone mass at the spine and lower bone turnover rates, both factors that translate to reductions in fracture risk. Fracture risk at the spine and hip increases 26 and 55% after breast cancer diagnosis, respectively [4], and both fracture types are associated with excess mortality and morbidity [59, 60]. Fractures in BCS add to the economic and personal costs that already result from treatment aimed to eradicate disease, particularly for older women [61, 62]. Our POWIR program was able to preserve bone and slow turnover and each could contribute to lower fracture risk at the spine. A 1–2% increase in BMD translates to a 7–14% decrease in fracture risk [63] and slowing of bone turnover can lower fracture risk at the hip and spine independent of BMD [64]. It was encouraging that the training effect on spine BMD and turnover were independent of adjuvant hormone therapy use so that women on bone-depleting AIs still benefited from exercise. Whether exercise can offer a lifestyle strategy to reduce hip fracture risk by preserving bone mass at the hip in BCS remains unclear.

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References

1. Horner, MJ.; Ries, LAG.; Krapcho, M.; Neyman, N.; Aminou, R.; Howlader, N.; Altekruse, SF.; Feuer, EJ.; Huang, L.; Mariotto, A.; Miller, BA.; Lewis, DR.; Eisner, MP.; Stinchcomb, DG.; Edwards, BK. SEER cancer statistics review, 1975–2006. National Cancer Institute; 2009. http://seer.cancer.gov/csr/1975_2006/. Posted to the SEER web site, 2009
2. Chen Z, Maricic M, Bassford TL, Pettinger M, Ritenbaugh C, Lopez AM, Barad DH, Gass M, Leboff MS. Fracture risk among breast cancer survivors: results from the Women's Health Initiative Observational Study. *Arch Int Med*. 2005; 165(5):552–558. [PubMed: 15767532]
3. Kanis JA, McCloskey EV, Powles T, Paterson AH, Ashley S, Spector T. A high incidence of vertebral fracture in women with breast cancer. *Br J Cancer*. 1999; 79(7–8):1179–1181. [PubMed: 10098755]
4. Chen ZMM, Aragaki AK, Mouton C, Arendell L, Lopez AM, Bassford T, Chlebowski RT. Fracture risk increases after diagnosis of breast or other cancers in postmenopausal women: results from the Women's Health Initiative. *Osteoporos Int*. 2009; 20(4):527–536. [PubMed: 18766294]
5. Stearns V, Schneider B, Henry NL, Hayes DF, Flockhart DA. Breast cancer treatment and ovarian failure: risk factors and emerging genetic determinants. *Nat Rev Cancer*. 2006; 6(11):886–893. [PubMed: 17036039]
6. Friedlaender GE, Tross RB, Doganis AC, et al. Effects of chemotherapeutic agents on bone. *Bone Joint Surgery*. 1984; 66A:602–607.
7. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. *J Clin Oncol*. 2001; 19(14):3306–3311. [PubMed: 11454877]
8. Cameron D, Douglas S, Brown J, Anderson R. Bone mineral density loss during adjuvant chemotherapy in pre-menopausal women with early breast cancer: is it dependent on oestrogen deficiency? *Breast Cancer Res Treat*. 2010; 23(3):805–814. [PubMed: 20686833]
9. Greep NC, Giuliano AE, Hansen NM, Taketani T, Wang H-J, Singer FR. The effects of adjuvant chemotherapy on bone density in postmenopausal women with early breast cancer. *Am J Med*. 2003; 114(8):653–659. [PubMed: 12798453]
10. Coleman RE, Body J-J, Gralow JR, Lipton A. Bone loss in patients with breast cancer receiving aromatase inhibitors and associated treatment strategies. *Cancer Treat Rev*. 2008; 34(Suppl 1):S31–S42. [PubMed: 18486346]
11. Winters-Stone KM, Bennett JA, Nail L, Schwartz A. Strength, physical activity, and age predict fatigue in older breast cancer survivors. *Oncol Nurs Forum*. 2008; 35(5):815–821. [PubMed: 18765328]
12. Respini D, Jacobsen PB, Thors C, Tralongo P, Balducci L. The prevalence and correlates of fatigue in older cancer patients. *Crit Rev Oncol Hematol*. 2003; 47(3):273–279. [PubMed: 12962901]
13. Freedman RJ, Aziz N, Albanes D, Hartman T, Danforth D, Hill S, Sebring N, Reynolds JC, Yanovski JA. Weight and body composition changes during and after adjuvant chemotherapy in women with breast cancer. *J Clin Endocrinol Metab*. 2004; 89(5):2248–2253. [PubMed: 15126549]
14. Demark-Wahnefried W, Peterson BL, Winer EP, Marks L, Aziz N, Marcom PK, Blackwell K, Rimer BK. Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol*. 2001; 19(9):2381–2389. [PubMed: 11331316]

15. Aslani A, Smith RC, Allen BJ, Pavlakis N, Levi JA. Changes in body composition during breast cancer chemotherapy with the CMF-regimen. *Breast Cancer Res Treat.* 1999; 57(3):285–290. [PubMed: 10617305]
16. Campbell KL, Lane K, Martin AD, Gelmon KA, McKenzie DC. Resting energy expenditure and body mass changes in women during adjuvant chemotherapy for breast cancer. *Cancer Nurs.* 2007; 30(2):95–100. [PubMed: 17413774]
17. Thomson CATP, Wright-Bea J, Nardi E, Frey GR, Stopeck A. Metabolic syndrome and elevated C-reactive protein in breast cancer survivors on adjuvant hormone therapy. *J Womens Health.* 2009; 18(12):2041–2047.
18. Kumar NB, Cantor A, Allen K, Cox CE. Android obesity at diagnosis and breast carcinoma survival: Evaluation of the effects of anthropometric variables at diagnosis, including body composition and body fat distribution and weight gain during life span, and survival from breast carcinoma. *Cancer.* 2000; 88(12):2751–2757. [PubMed: 10870057]
19. Monfardini S, Basso U. Oncological causes of frailty in older cancer patients. *Eur J Cancer.* 2007; 43(8):1230–1231. [PubMed: 17434302]
20. Hillner BE, Ingle JN, Berenson JR, Janjan NA, Albain KS, Lipton A, Yee G, et al. American Society of Clinical Oncology Guidelines on the role of bisphosphonates in breast cancer. *J Clin Oncol.* 2000; 18:1378–1391. [PubMed: 10715310]
21. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, Irwin ML, Wolin KY, Segal RJ, Lucia A, Schneider CM, von Gruenigen VE, Schwartz AL. American college of sports medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc.* 2010; 42(7):1409–1426. [PubMed: 20559064]
22. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv.* 2010; 4(2):87–100. [PubMed: 20052559]
23. Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling VR. American College of Sports Medicine Position Stand: physical activity and bone health. *Med Sci Sports Exerc.* 2004; 36(11):1985–1996. [PubMed: 15514517]
24. Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, Macera CA, Castaneda-Sceppa C. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc.* 2007; 39(8):1435–1445. [PubMed: 17762378]
25. Warden SJ, Fuchs RK, Turner CH. Steps for targeting exercise towards the skeleton to increase bone strength. *Eura Medicophys.* 2004; 40(3):223–232. [PubMed: 16172590]
26. Turner CH, Robling AG. Designing exercise regimens to increase bone strength. *Exerc Sport Sci Rev.* 2003; 31(1):45–50. [PubMed: 12562170]
27. Winters-Stone KM, Schwartz A, Nail LM. A review of exercise interventions to improve bone health in adult cancer survivors. *J Cancer Surviv.* 2010; 4(3):187–201. [PubMed: 20373041]
28. Hintze, J. PASS 6.0 power analysis and sample size for windows. NCSS; Keyville, Utah: 1996.
29. Winters KM, Snow CM. Detraining reverses positive effects of exercise on the musculoskeletal system in premenopausal women. *J Bone Miner Res.* 2000; 15:2495–2503. [PubMed: 11127215]
30. Shaw JM, Snow CM. Weighted vest exercise improves indices of fall risk in older women. *J Gerontol.* 1998; 53:M53–M58.
31. Winters-Stone K, Snow C. Site-specific response of bone to exercise in premenopausal women. *Bone.* 2006; 39(6):1203–1209. [PubMed: 16876495]
32. Snow CM, Shaw JM, Winters KM, Witzke KA. Long-term exercise using weighted vests prevents hip bone loss in post-menopausal women. *J Gerontol A Biol Sci Med Sci.* 2000; 55(9):M489–M491. [PubMed: 10995045]
33. Kraemer WJ, Adams K, Cafarelli E, Dudley GA, Dooly C, Feigenbaum MS, Fleck SJ, Franklin B, Fry AC, Hoffman JR, Newton RU, Pottenger J, Stone MH, Ratamess NA, Triplett-McBride T. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc.* 2002; 34(2):364–380. [PubMed: 11828249]
34. American College of Sports Medicine Position Stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc.* 2009; 41(3):687–708. [PubMed: 19204579]

35. Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, Skinner JS. American College of Sports Medicine position stand. Exercise and physical activity for older adults. *Med Sci Sports Exerc.* 2009; 41(7):1510–1530. [PubMed: 19516148]
36. Martyn-St James M, Carroll S. A meta-analysis of impact exercise on postmenopausal bone loss: the case for mixed loading exercise programmes. *Br J Sports Med.* 2009; 43(12):898–908. [PubMed: 18981037]
37. Bicego D, Brown K, Ruddick M, Storey D, Wong C, Harris SR. Exercise for women with or at risk for breast cancer-related lymphedema. *Phys Ther.* 2006; 86(10):1398–1405. [PubMed: 17012644]
38. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987; 40(5):373–383. [PubMed: 3558716]
39. Stewart A, Mills K, King A, Haskell W, Gillis D, Ritter P. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med Sci Sports Exerc.* 2001; 33(7):1126–1141. [PubMed: 11445760]
40. Binkley N, Bilezikian JP, Kendler DL, Leib ES, Lewiecki EM, Petak SM. Summary of the International Society for Clinical Densitometry 2005 position development conference. *J Bone Miner Res.* 2007; 22(5):643–645. [PubMed: 17280530]
41. Raudenbush, S.; Bryk, A. Hierarchical linear models: applications and data analysis methods. 2. Sage Publications; Thousand Oaks: 2002.
42. Lane P. Handling drop-out in longitudinal clinical trials: a comparison of the LOCF and MMRM approaches. *Pharm Stat.* 2008; 7:93–106. [PubMed: 17351897]
43. Streiner DL. The case of the missing data: methods of dealing with dropouts and other research vagaries. *Can J Psychiatry.* 2002; 47:68–75. [PubMed: 11873711]
44. Ravn P, Thompson DE, Ross PD, Christiansen C. Biochemical markers for prediction of 4-year response in bone mass during bisphosphonate treatment for prevention of postmenopausal osteoporosis. *Bone.* 2003; 33(1):150–158. [PubMed: 12919710]
45. Bassey E, Rothwell M, Littlewood J, Pye D. Pre- and postmenopausal women have different bone mineral density responses to the same high-impact exercise. *J Bone Miner Res.* 1998; 13(12):1805–1813. [PubMed: 9844097]
46. Bassey E, Ramsdale S. Weight-bearing exercise and ground reaction forces: a 12-month randomized controlled trial of effects on bone mineral density in healthy postmenopausal women. *Bone.* 1995; 16:469–476. [PubMed: 7605708]
47. Kohrt W, Ehsani A, Birge S. Effects of exercise involving predominantly either joint-reaction or ground-reaction forces on bone mineral density in older women. *J Bone Min Res.* 1997; 12:1253–1261.
48. Going S, Lohman T, Houtkooper L, Metcalfe L, Flint-Wagner H, Blew R, Stanford V, Cussler E, Martin J, Teixeira P, Harris M, Milliken L, Figueroa-Galvez A, Weber J. Effects of exercise on bone mineral density in calcium-replete postmenopausal women with and without hormone replacement therapy. *Osteoporos Int.* 2003; 14(8):637–643. [PubMed: 12844212]
49. Kerr D, Ackland T, Maslen B, Morton A, Prince R. Resistance training over 2 years increases bone mass in calcium-replete postmenopausal women. *J Bone Miner Res.* 2001; 16(1):175–181. [PubMed: 11149482]
50. Schmitz KH, Ahmed RL, Hannan PJ, Yee D. Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. *Cancer Epidemiol Biomarkers Prev.* 2005; 14(7):1672–1680. [PubMed: 16030100]
51. Schmitz KH, Ahmed RL, Troxel A, Cheville A, Smith R, Lewis-Grant L, Bryan CJ, Williams-Smith CT, Greene QP. Weight lifting in women with breast-cancer-related lymphedema. *New Engl J Med.* 2009; 361(7):664–673. [PubMed: 19675330]
52. Schmitz KH, Ahmed RL, Troxel AB, Cheville A, Lewis-Grant L, Smith R, Bryan CJ, Williams-Smith CT, Chittams J. Weight lifting for women at risk for breast cancer-related lymphedema. *JAMA.* 2010; 304(24):2699–2705. [PubMed: 21148134]
53. van Londen G, Perera S, Vujevich K, Rastogi P, Lembersky B, Brufsky A, Vogel V, Greenspan S. The impact of an aromatase inhibitor on body composition and gonadal hormone levels in women with breast cancer. *Breast Cancer Res Treat.* 2011; 125(2):441–446. [PubMed: 21046232]

54. Kenny AM, Boxer RS, Kleppinger A, Brindisi J, Feinn R, Burleson JA. Dehydroepiandrosterone combined with exercise improves muscle strength and physical function in frail older women. *J Am Geriatr Soc.* 2010; 58(9):1707–1714. [PubMed: 20863330]
55. Martyn-St James M, Carroll S. Meta-analysis of walking for preservation of bone mineral density in postmenopausal women. *Bone.* 2008; 43(3):521–531. [PubMed: 18602880]
56. Irwin ML, Alvarez-Reeves M, Cadmus L, Mierzejewski E, Mayne ST, Yu H, Chung GG, Jones B, Knobf MT, DiPietro L. Exercise improves body fat, lean mass, and bone mass in breast cancer survivors. *Obesity (Silver Spring).* 2009; 17(8):1534–1541. [PubMed: 19629060]
57. Twiss JJ, Waltman NL, Berg K, Ott CD, Gross GJ, Lindsey AM. An exercise intervention for breast cancer survivors with bone loss. *J Nurs Scholarsh.* 2009; 41(1):20–27. [PubMed: 19335674]
58. Reginster JY, Rabenda V, Neuprez A. Adherence, patient preference and dosing frequency: understanding the relationship. *Bone.* 2006; 38(4):S2–S6. [PubMed: 16520104]
59. Morin S, Lix L, Azimae M, Metge C, Caetano P, Leslie W. Mortality rates after incident non-traumatic fractures in older men and women. *Osteoporos Int.* 2010:1–10.
60. Boonen S, Singer AJ. Osteoporosis management: impact of fracture type on cost and quality of life in patients at risk for fracture I. *Curr Med Res Opin.* 2008; 24(6):1781–1788. [PubMed: 18489813]
61. Robb C, Haley WE, Balducci L, Extermann M, Perkins EA, Small BJ, Mortimer J. Impact of breast cancer survivorship on quality of life in older women. *Crit Rev Oncol Hematol.* 2007; 62(1):84–91. [PubMed: 17188505]
62. Zhou Z, Redaelli A, Johnell O, Willke RJ, Massimini G. A retrospective analysis of health care costs for bone fractures in women with early-stage breast carcinoma. *Cancer.* 2004; 100(3):507–517. [PubMed: 14745866]
63. Wasnich RD, Miller PD. Antifracture efficacy of antiresorptive agents are related to changes in bone density. *J Clin Endocrinol Metab.* 2000; 85(1):231–236. [PubMed: 10634392]
64. Garnero P. Biomarkers for osteoporosis management: utility in diagnosis, fracture risk prediction and therapy monitoring. *Mol Diag Ther.* 2008; 12(3):157–170.

Fig. 1.
Participant flow from recruitment to analysis

Fig. 2. Pattern of changes in spine and hip BMD (g/cm²) in FLEX and POWIR across the 12-month intervention for participants with complete data sets for all time points

Fig. 3. Changes in bone-free lean mass over 12 months by exercise group between current users of AI and non-users using predicted means from HLM analyses

Table 1

Planned progression of training in POWIR over 12 months^a

Month	Jump			Lower body			Upper body		
	Intensity	Sets	Reps	Intensity	Sets	Reps	Intensity	Sets	Reps
1	None	None	None	0% BW	1-2	8-12	13-15 RM	1-2	12-14
2	0-1% BW	1-2	10	1-3% BW	1-2	8-12	11-13 RM	1-2	10-12
3	1-3% BW	3-4	10	3-5% BW	1-2	8-12	9-11 RM	1-2	8-10
4-6	3-7% BW	5-6	10	5-10% BW	1-2	8-12	8-10 RM	1-2	6-8
7-9	7-10% BW	6	10	10-15% BW	1-2	8-12	8-10 RM	1-2	8-10
10-12	10% BW	6	10	15% BW	1-2	8-12	8-10 RM	1-2	8-10

^aIntensity for jumps and lower body exercises set as a % of body weight (BW) loaded into weighted vests. Intensity for upper body exercises set as a Repetition Maximum (RM); the number of repetitions completed at a set weight. Higher RM indicates a lower workload (participant is doing lower weight for more repetitions) and a lower RM indicates a higher workload

Table 2

Baseline clinical characteristics of participants of who were randomized

Characteristic	POWIR (N = 52)	FLEX (N = 54)
	Mean (SD) or % of sample	Mean (SD) or % of sample
Age (years)	62.3 (6.7)	62.2 (6.7)
Comorbidity index	1.9 (1.7)	1.6 (1.7)
BMI (kg/m ²)	29.5 (5.8)	29.5 (5.6)
Spine (L ₁ –L ₄) T-score ^a	−0.52 (1.2)	−0.55 (0.99)
Femoral neck T-score ^a	−0.96 (0.86)	−1.01 (0.82)
FSH (IU)	82.3 (36.0)	69.1 (32.0)
Estradiol (pg/ml)	5.7 (2.9)	7.6 (4.0)
Time since diagnosis (months)	56.5 (39.9)	64.5 (35.4)
Stage 0 (%)	7.7%	3.7%
Stage I (%)	38.5%	40.7%
Stage II (%)	48.1%	35.2%
Stage IIIa (%)	1.9%	9.3%
Received chemotherapy (%)	61.5%	59.3%
Received radiation therapy (%)	92.3%	83.3%
Currently taking AI (%)	42.3%	40.7%
Currently taking SERM (%)	17.3%	13.0%
Prior bisphosphonate use	5.8%	5.6%

Data are expressed as mean (SD) for continuous data or % of sample for categorical data

AI Aromatase inhibitor, SERM selective estrogen receptor modulator

^aT-scores are reported for the lumbar spine and femoral neck. The WHO recommends the femoral neck site be used for diagnosing osteoporosis in women, but acknowledges that other skeletal sites may be considered for clinical decision making

Table 3

Initial and final values on primary outcomes and covariates by exercise group from baseline to 12 months

Characteristic	POWIR (n = 36)		FLEX (n = 31)		F(df)*	P value*
	Baseline Mean (SD)	12 Months Mean (SD)	% Change	Baseline Mean (SD)	12 Months Mean (SD)	% Change
Body weight	75.6 (15.5)	76.5 (15.6)	1.19	74.0 (12.3)	74.2 (12.3)	0.27
Bone-free lean mass (kg)	43.4 (6.5)	44.0 (6.7)	1.38	44.7 (5.8)	45.2 (6.0)	1.12
Fat mass (kg)	30.4 (9.4)	30.9 (9.7)	1.64	29.0 (8.2)	29.0 (8.1)	0.00
% Body fat	40.5 (5.7)	40.5 (6.2)	0.00	38.7 (5.6)	38.5 (5.8)	-0.52
Spine (L ₁ -L ₄) BMD (g/cm ²)	0.983 (0.146)	0.987 (0.146)	0.41	0.971 (0.120)	0.949 (0.108)	-2.27
Total hip BMD (g/cm ²)	0.863 (0.101)	0.860 (0.105)	-0.35	0.848 (0.099)	0.841 (0.096)	-0.83
Greater trochanter BMD (g/cm ²)	0.657 (0.088)	0.654 (0.087)	-0.46	0.642 (0.091)	0.641 (0.089)	-0.156
Femoral neck BMD (g/cm ²)	0.731 (0.100)	0.721 (0.101)	-1.37	0.728 (0.091)	0.713 (0.082)	-2.06
Osteocalcin (ng/ml) ^a	12.6 (4.4)	12.8 (3.8)	1.59	11.3 (4.1)	14.3 (5.0)	26.5
Deoxypyridinoline (nmol/nmolCr)	21.4 (9.8)	13.1 (4.2)	-38.8	17.1 (5.6)	12.2 (3.1)	-28.7
Energy expenditure (kcal/d) ^b	434.3 (300.1)	430.8 (281.4)	-0.81	458.9 (346.4)	461.7 (346.4)	0.61
Energy intake (kcal/d)	1331.2 (449.5)	1347.6 (441.2)	1.23	1549.6 (553.4)	1501.6 (557.0)	-3.10
Calcium intake (mg/day) ^c	694.6 (333.9)	751.0 (356.8)	8.12	797.1 (294.1)	723.6 (297.9)	-9.22

Data presented as unadjusted mean (SD) for participants with complete data sets for both time points

* F and P value (using Huynh-Feldt adjustment for sphericity) from RM-ANCOVA for the time by group interaction that included baseline, 6 and 12 month time points and controlled for the following: age, time since diagnosis, current adjuvant hormone therapy use. P values are observed and not corrected for multiple testing

^a Sample size for biomarkers was N = 33 for POWIR and N = 28 for FLEX

^b Energy expenditure calculated from CHAMPS physical activity survey and includes energy expended in activities ranging from low to vigorous intensity per week

^c Calcium intake includes calcium obtained both from dietary sources and from dietary supplements