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A Randomized Trial of Exercise and Diet on Body Composition in Survivors of Breast Cancer with Overweight or Obesity

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Author Contributions

Conception and design of study (JCB, DBS, ABT, KS, AMD, CSD, KHS); acquisition of data (JCB, DBS, KS, AMD, CSD, KHS); analysis and/or interpretation of data (JCB, DBS, ABT, KS, KHS); drafting the manuscript (JCB, KHS); approval of the version of the manuscript to be published (JCS, DBS, ABT, KS, AMD, CSD, KHS).

Conflicts of Interest/Competing Interests

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Availability of data and material

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Yes

Consent to Participate

Yes

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Abstract

Purpose: Obesity increases the risk of cancer recurrence and death in survivors of breast cancer. This study tested the hypothesis that exercise alone, diet alone, and the combination of exercise plus diet reduce body weight and improve body composition in survivors of breast cancer.

Methods: In this 2×2 factorial trial, 351 survivors of breast cancer with overweight or obesity were randomized to one of four treatment groups for 52 weeks: control, exercise alone, diet alone, or exercise plus diet. Endpoints included body weight and body composition measured by dual-energy x-ray absorptiometry.

Results: After 52 weeks, compared with control, diet alone [−5.39 kg (95% CI: −7.24, −3.55); −6.0% (95% CI: −8.0, −3.9)] and exercise plus diet [−6.68 kg (95% CI: −8.46, −4.90); −7.4% (95% CI: −9.4, −5.4)] reduced body weight; exercise alone did not change body weight. Compared with control, diet alone [−3.59 kg (95% CI: −5.00, −2.17)] and exercise plus diet [−4.28 kg (95% CI: −5.71, −2.84)] reduced fat mass; exercise alone did not change fat mass. Compared with control, diet alone [−0.82 kg (95% CI: −1.50, −0.15)] and exercise plus diet [−1.24 kg (95% CI: −1.92, −0.56)] reduced lean mass; exercise alone did not change lean mass. Compared with control, exercise alone, diet alone, and exercise plus diet did not change bone mineral density.

Conclusion: In survivors of breast cancer with overweight or obesity, diet alone or diet plus exercise produced clinically meaningful weight loss at week 52. The majority of weight loss was fat mass.

Keywords

adipose tissue; bone density; diet therapy; exercise; muscle

INTRODUCTION

Obesity is a chronic, relapsing, and progressive disease that is characterized by excess adiposity [1]. One-in-three survivors of breast cancer has obesity [2]. Obesity increases the risk of cancer recurrence and death in survivors of breast cancer [3, 4]. Moreover, obesity increases the risk of competing causes of morbidity and mortality, such as type 2 diabetes and cardiovascular disease [5-7].

Multimodal lifestyle interventions that include diet modification, increased physical activity, and lifestyle modification instruction are the foundation of obesity care [8]. Multimodal lifestyle interventions report 3–5% weight loss in survivors of breast cancer [9, 10]. In the general population, hypocaloric diets reduce body fat but catabolize lean tissue [11, 12].

Quantifying how fat and lean tissues change in response to lifestyle intervention is clinically relevant as excess fat mass and low lean mass are each independently associated with an increased risk of death in survivors of breast cancer [13]. Excess fat mass increases the risk of cancer recurrence, type 2 diabetes, and cardiovascular disease [14, 15]. In contrast, low lean mass increases the risk of frailty, falls, and functional decline [16]. Moreover, weight loss may reduce bone mineral density [17].

These observations provided the rationale to test the hypothesis that exercise alone, diet alone, and the combination of exercise plus diet reduce body weight and improve body composition, as compared with control, in survivors of breast cancer. To our knowledge, this study is the first to report the effects of distinct lifestyle interventions on measures of body composition in survivors of breast cancer with overweight or obesity. We previously reported that exercise and diet did not improve the primary endpoint of breast cancer-related lymphedema assessed by interlimb volume difference [18]. This trial used a 2×2 factorial design, which allowed the comprehensive examination of exercise and diet. This trial was sponsored by the National Cancer Institute (NCI) as part of the Transdisciplinary Research on Energetics and Cancer (TREC) consortium [19].

METHODS

Study Design

This study was a 52-week, randomized, 2×2 factorial trial. The study was conducted in accordance with Good Clinical Practice and the ethical principles originating in the Declaration of Helsinki. The Institutional Review Board approved the protocol and the informed consent document. All participants provided written informed consent and approval from their physician to enroll in the study. The study is registered on ClinicalTrials.gov as NCT01515124. The trial design is described in detail elsewhere [20].

Participants

Eligible participants had stage I-III breast cancer; completed surgery, chemotherapy, radiotherapy, and targeted therapy ≥6 months before study enrollment (concurrent endocrine therapy was allowed); had a body mass index (BMI) of 25–50 kg/m^2; had breast cancer related lymphedema, defined using the Common Terminology Criteria for Adverse Events (CTCAE; version 4) [21], or a prior clinical diagnosis of lymphedema; and were aged 18–80 years. In addition, eligible participants had no evidence of residual or recurrent cancer; no medical conditions that would preclude participation in an exercise or diet program; were not engaging in any resistance exercise or ≥3 bouts of aerobic exercise of moderate intensity (e.g., brisk walking) weekly over the prior 52 weeks; were not using any medications for the purpose of weight loss; had no weight loss ≥4.5 kg in the previous 12 weeks; and had no history of bariatric or metabolic surgery. Participants were recruited using a variety of active and passive outreach methods [22].

Randomization and Blinding

Participants were assigned in an equal ratio to one of four treatment groups for 52 weeks: control, exercise alone, diet alone, or exercise plus diet. Participants were stratified by age, the number of lymph nodes resected during breast cancer surgery, receipt of radiotherapy, lymphedema severity, and body mass index and then randomized using a computerized covariate adaptive procedure [23]. Participants were not blinded to treatment assignment. Endpoint measures were obtained by certified staff members who were blinded to treatment assignment.

Control Treatment Condition

Participants assigned to the control group were instructed to refer to their physician regarding what types of exercise or diet would be safe and effective. No other guidance regarding exercise or diet was provided.

Exercise Treatment Condition

Participants assigned to the exercise group performed a combination of in-person and home-based exercise. Exercise modalities included resistance and aerobic activity, consistent with recommendations from the American College of Sports Medicine [24]. In-person exercise, supervised by an exercise oncology professional, occurred weekly in the first six weeks of the study, and once per month thereafter in groups of 2–6 participants. Participants performed resistance exercise using adjustable dumbbell weights (PowerBlock, Inc) that were provided by the study and were delivered to participant's residence. The resistance program included nine exercises that were performed twice weekly for 2–3 sets using a weight that permitted 10 repetitions with proper form and didn't exacerbate lymphedema symptoms; the resistance exercise prescription was adapted from the 'Physical Activity and Lymphedema' (PAL) trial [25, 26]. Moderate-intensity aerobic exercise was prescribed to a goal of 180 minutes weekly distributed over 3–6 days per week (e.g., 30 minutes on most days of the week). The detailed exercise treatment plan is published elsewhere [20].

Diet Treatment Condition

Participants assigned to the diet group attended 24 weekly sessions of lifestyle modification instruction led by a registered dietitian in groups of 2–12 participants. The goal of the diet was a 10% loss of body weight. Weekly counseling sessions included a weigh-in, review of the week, and behavioral modification lesson (e.g., self-monitoring, goal setting, stimulus control). During the first 20 weeks, participants followed a meal replacement program (Nutrisystem, Inc) that also included seven daily servings of fruits and vegetables, consistent with the American Cancer Society recommendations [27]. During weeks 21–24, the focus shifted to applying the behavioral modification techniques to food shopping and preparation. During weeks 24–52, the groups met in-person monthly for additional behavioral modification lessons (e.g., problem-solving, relapse prevention). Behavior modification lessons were adapted from the 'Improving the Management of Obesity in Primary Care' (POWER-UP) trial [28]. The detailed diet treatment plan is published elsewhere [20].

Combined Exercise Plus Diet Treatment Condition

Participants assigned to the exercise plus diet group started with six weeks of exercise instruction. At week seven, they began receiving the diet intervention in addition to the exercise intervention. Thereafter, participants received the exercise and diet interventions simultaneously.

Body Composition Endpoint Measures

Assessment of anthropometric and body composition measures followed standardized procedures. Participants wore a medical gown and were asked to remove their shoes, and all jewelry or other personal effects. Height was measured using a wall-mounted stadiometer. Weight was measured in duplicate using a calibrated digital scale; a third measurement was obtained if the difference of the first two measures exceeded 0.5 kg. Body composition was measured with whole-body dual-energy x-ray absorptiometry (DXA; Hologic Inc). All images were reviewed for quality assurance by a certified DXA technician who was blinded to treatment assignment. The DXA scanner was calibrated at regular intervals using spine and whole-body tissue phantoms. The DXA analysis was used to calculate fat mass (kg), visceral adipose tissue (cm^2), subcutaneous adipose tissue (cm^2), lean mass (kg), appendicular lean mass (kg), and bone mineral density (g/cm^2) using APEX v.13.5 software. Appendicular lean mass is a surrogate for muscle mass because lean tissue in the arms and legs is striated and does not include cardiac and smooth muscle or other organs (which is included in the calculation of total lean mass) [29]. The validation and precision of DXA against whole-body computed tomography and magnetic resonance imaging has been reported [30, 31].

Other Measures

Demographic characteristics, including age, race, and education, were self-reported. Clinical characteristics, including time since breast cancer diagnosis, cancer stage, number of resected lymph nodes, and treatment types were abstracted from a combination of pathology reports and other physician records. Arm volume was measured by perometry [32].

Statistical Analysis

The sample size was selected to provide sufficient statistical power to detect change in the primary endpoint of breast cancer-related lymphedema interlimb volume difference [18]. Based on estimates from the Action for Health in Diabetes (Look AHEAD) [11] and the Nutrition and Exercise in Women (NEW) trials [33], this study had 80% statistical power to detect standardized mean difference effect sizes of ≥0.18 using two-sided 0.05-level tests.

The statistical analysis included all participants who were randomly assigned, and all available in-trial data at week 52 were included in accordance with the intention-to-treat principle. Intrial data at week 52 included both adherent participants and retrieved participants who prematurely discontinued their assigned intervention. Missing data at week 52 were imputed using predictive mean matching multiple imputation with 20 imputation replicates [34]. The primary contrast quantified the effect of each of the three intervention groups (exercise alone, diet alone, and exercise plus diet) with the control group, using a sequentially rejective testing procedure [35]. Continuous endpoints were analyzed using an analysis of covariance model that included group-by-time interaction terms, dependent variable’s baseline value, and randomization stratification factors [36]. Relative change in body weight was calculated using the estimated absolute treatment effect and mean baseline body weight. The categorical endpoints of ≥5% and ≥10% loss of body weight were analyzed using a logistic regression model with multiple imputation. All statistical testing was two-sided. Analyses were done using Stata/MP v.15.1 (StataCorp, LLC).

RESULTS

Between December 2011 and April 2015, 351 participants were randomized, with endpoint data collection ending in May 2016. Study participants had a mean (SD) age of 59.4 (8.7) years, 133 (38%) were non-white, and 165 (47%) completed a four-year college degree (Table 1).

At baseline, the mean body weight was 90.0 (16.4) kg, and BMI was 34.0 (5.9) kg/m^2; 243 (69%) participants had obesity (BMI ≥30 kg/m^2), of whom 141 (58%) had severe obesity (BMI ≥35 kg/m^2). At 52 weeks, 275 (78%) of participants provided body composition endpoint data (Figure 1). Participants who did not provide endpoint data were more likely to be recently diagnosed with cancer [multivariable-adjusted odds ratio: 1.03 per five-year interval (95% CI: 1.00, 1.07)]; no other measured baseline factors, including randomized group assignment (P=0.46) and body weight (P=0.74), were associated with missing week 52 endpoint data. Participants randomized exercise alone or exercise plus diet attended 84% of in-person supervised exercise sessions; adherence did not differ between exercise alone or exercise plus diet [Δ: −1.0% (95% CI: −7.3, 5.3)]. Participants randomized to diet alone or exercise plus diet attended 74% of in-person lifestyle modification sessions; adherence did not differ between diet alone or exercise plus diet [Δ: 0.9% (95% CI: −7.3, 9.1)].

Body Weight

At 52 weeks, compared with control, diet alone [−5.39 kg (95% CI: −7.24, −3.55); −6.0% (95% CI: −8.0, −3.9); −2.1 kg/m^2 (95% CI: −2.8, −1.4)] and exercise plus diet [−6.68 kg (95% CI: −8.46, −4.90); −7.4% (95% CI: −9.4, −5.4); −2.5 kg/m^2 (95% CI: −3.2, −1.8)] reduced body weight (Table 2); exercise alone did not change body weight [−0.06 kg (95% CI: −1.85, 1.72); −0.1% (95% CI: −2.1, 1.9); −0.1 kg/m^2 (95% CI: −0.7, 0.7)]. Compared with control, diet alone [0.49 (95% CI: 0.35, 0.62)] and exercise plus diet [0.46 (95% CI: 0.31, 0.60)] increased the probability of achieving ≥5% loss of baseline body weight (Figure 2); exercise alone did not increase the probability of achieving ≥5% loss of baseline body weight [0.01 (95% CI: −0.11, 0.12)]. Compared with control, diet alone [0.26 (95% CI: 0.15, 0.37)] and exercise plus diet [0.39 (95% CI: 0.26, 0.51)] increased the probability of achieving ≥10% loss of baseline body weight; exercise alone did not increase the probability of achieving ≥10% loss of baseline body weight [0.02 (95% CI: −0.06, 0.10)].

Adipose Tissue

At 52 weeks, compared with control, diet alone [−3.59 kg (95% CI: −5.00, −2.17)] and exercise plus diet [−4.28 kg (95% CI: −5.71, −2.84)] reduced fat mass; exercise alone did not change fat mass [0.14 kg (95% CI: −1.30, 1.59)]. Compared with control, diet alone [−21.28 cm^2 (95% CI: −31.37, −11.19)] and exercise plus diet [−19.87 cm^2 (95% CI: −30.03, −9.70)] reduced visceral adipose tissue area; exercise alone did not change visceral adipose tissue area [−5.50 cm^2 (95% CI: −15.73, 4.73)]. Compared with control, diet alone

[−39.53 cm^2 (95% CI: −59.85, −19.23)] and exercise plus diet [−45.19 cm^2 (95% CI: −65.14, −25.23)] reduced subcutaneous adipose tissue area; exercise alone did not change subcutaneous adipose tissue area [7.69 cm^2 (95% CI: −12.20, 27.58)].

Lean Mass

At 52 weeks, compared with control, diet alone [−0.82 kg (95% CI: −1.50, −0.15)] and exercise plus diet [−1.24 kg (95% CI: −1.92, −0.56)] reduced lean mass; exercise alone did not change lean mass [0.42 kg (95% CI: −0.25, 1.10)]. Compared with control, diet alone [−0.32 kg (95% CI: −0.63, −0.01)] and exercise plus diet [−0.46 kg (95% CI: −0.77, −0.15)] reduced appendicular lean mass; exercise alone did not change appendicular lean mass [0.23 kg (95% CI: −0.08, 0.54)].

Bone Density

At 52 weeks, compared with control, exercise alone [−0.001 g/cm^2 (95% CI: −0.012, 0.010)], diet alone [0.005 g/cm^2 (95% CI: −0.006, 0.016)], and exercise plus diet [0.003 g/cm^2 (95% CI: −0.008, 0.014)] did not change bone mineral density.

Adverse Events

No serious or unexpected adverse events were reported; nonserious adverse events have been described [18].

DISCUSSION

In this 2×2 factorial trial of survivors of breast cancer with overweight or obesity, randomization to 52 weeks of diet or exercise plus diet produced statistically significant and clinically meaningful reductions in body weight, total body fat, and visceral adipose tissue. The majority of weight loss consisted of fat mass. Bone mineral density did not worsen in any intervention group over the 52-week treatment period, compared to the control group. The effects of exercise alone on body weight and body composition were nominal, and when combined with diet, did not mitigate the loss of lean mass.

The observed weight loss of 6.0% and 7.4% in the diet alone and exercise plus diet groups can be compared with the Lifestyle Intervention in Adjuvant Treatment of Early Breast Cancer (LISA) and Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) trials [9, 10]. The LISA trial reported that a telephone-based multimodal lifestyle intervention reduced body weight by 4.8% at week 52 [10]. The ENERGY trial reported that a group-based lifestyle intervention reduced body weight by 4.5% at week 52 [9]. The current trial used a meal replacement plan, which in the general population yield greater weight loss than lifestyle modification instruction alone [28].

The observed magnitude of weight loss may be clinically meaningful [8]. Each 5 kg/m^2 increase in BMI is associated with an 8–14% increase in the risk of disease recurrence or death in survivors of breast cancer [37, 38]. A hypothesis-generating analysis of the LISA trial demonstrated that randomization to the multimodal lifestyle intervention was associated with a numerically lower risk of cancer recurrence or death, as compared with control [HR:

0.71 (95% CI: 0.41, 1.24)] [39]. Weight loss ≥5% is associated with a 58% lower risk of developing type 2 diabetes [40], and weight loss ≥10% is associated with a 20% lower risk of experiencing a composite endpoint of major adverse cardiovascular events, including myocardial infarction, stroke, hospitalization for angina, and cardiovascular death [41].

In the general population, hypocaloric diets reduce body fat but catabolize lean tissue [12]. The Look AHEAD trial demonstrated that among patients with type 2 diabetes and obesity, reductions in body weight were composed of ≈70% fat mass [11]. In the current study, reductions in body weight were composed of 66% and 64% fat mass in the diet alone and the exercise plus diet groups, respectively. In a prior six-month study of weight loss in survivors of breast cancer, lean mass was not statistically significantly reduced from baseline, however the magnitude of weight loss was smaller (4.4%) than in our study making direct comparisons challenging [42]. These results confirm that the relative contribution of fat mass to weight loss in survivors of breast cancer is like other populations. Exercise, when combined with caloric restriction, did not substantively change the fraction of weight loss as fat mass, which is consistent with other studies [12].

Measures of body composition may offer additional information to quantify disease risk beyond that of body weight or BMI alone. Central adiposity, including visceral and subcutaneous adipose tissue, are strong predictors of adverse oncologic, metabolic, and cardiovascular outcomes [43]. Among survivors of breast cancer, excess subcutaneous adipose tissue is associated with a higher risk of all-cause death [44], and excess visceral adipose tissue is associated with a higher risk of myocardial infarction, stroke, and cardiovascular death [7]. The current trial demonstrated that diet alone and exercise plus diet induced statistically significant reductions in visceral and subcutaneous adipose tissue.

Critically low levels of lean mass, such as that occurring in old age, are associated with an increased risk of frailty, falls, and functional decline [16]. Over 52 weeks, participants in the diet alone and exercise plus diet groups lost 0.82 kg and 1.24 kg of lean mass, respectively; the relative changes were similar when restricted to appendicular lean mass as a surrogate for muscle mass. In randomized clinical trials of older adults with obesity, weight loss, with or without exercise, is associated with an improvement in objectively measured physical functioning [45, 46]. There were no detrimental effects of diet on bone mineral density. An ongoing randomized phase III trial will provide critical data needed to support the hypothesis that the overall health benefits of intentional and judicious weight loss in survivors of breast cancer outweigh the adverse effects of lean mass catabolism [47].

There are limitations to this trial. This trial was designed to evaluate the effects of two distinct, but complementary, lifestyle interventions; other trials included in the TREC consortium compared various combinations of exercise or diet with pharmacotherapy in survivors of cancer, thus we are unable to comment on lifestyle-pharmacotherapy synergy [19]. Unlike other modalities of body composition measurement, such as whole-body magnetic resonance imaging, DXA is unable to quantify intermuscular, hepatic, and pancreatic adipose tissue. Although the exercise group performed resistance and aerobic activities, the exercise program may have been of insufficient physiologic stimulus to meaningfully change body composition. Prior randomized trials of exercise that provided sufficient physiologic stimulus to change body composition outcomes included more supervision by exercise professionals, including the PAL trial [25, 26]. Missing endpoint data did not differ between randomized groups and was not associated with baseline body weight and body composition, however participants who did not provide endpoint data may differ in other ways that are not known. Although this study recruited participants with lymphedema, there is no reason to believe that these findings cannot be generalized to the broader population of survivors of breast cancer with overweight or obesity.

There are strengths to this trial. The randomized design and use of two distinct lifestyle modification interventions allowed for a time- and cost-efficient comparison of causal effects. The large sample size allowed us to detect small but potentially clinically important effect size differences. The diverse study sample improves the generalizability of study findings. The intervention was deployed using a combination of in-person and home-based methods. The diet program utilized a commercially available meal replacement program that is available throughout the United States. The use of home-based exercise reduced known barriers of participation associated with supervised gym-based programs.

Among survivors of breast cancer with overweight or obesity, diet alone or diet plus exercise produced clinically meaningful weight loss at week 52, with the majority of weight loss as fat mass. In conclusion, these data provide physiological support to the potential clinical benefits of weight management in survivors of breast cancer, for which phase III studies are ongoing [47].

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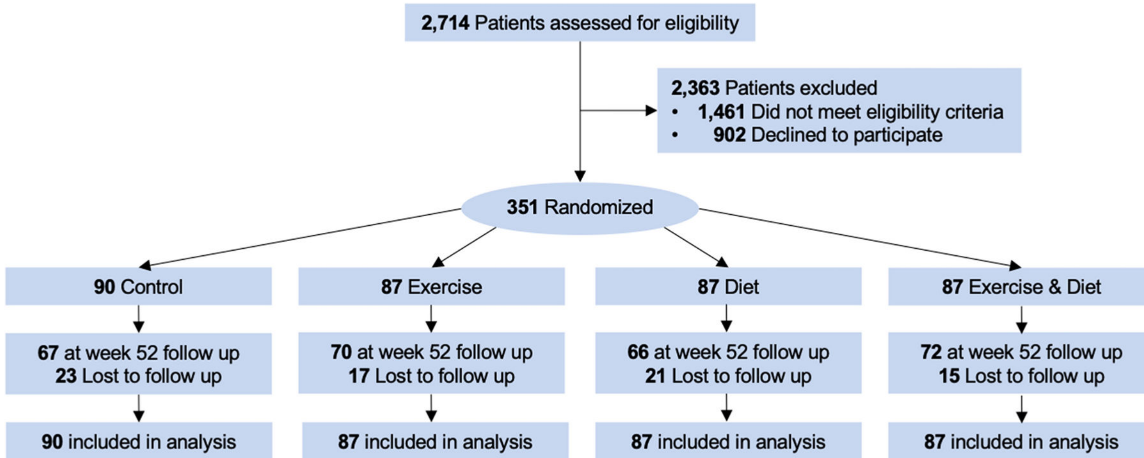

Figure 1.
Flow of participants and ascertainment of body composition endpoint measures at week 52 by randomized group

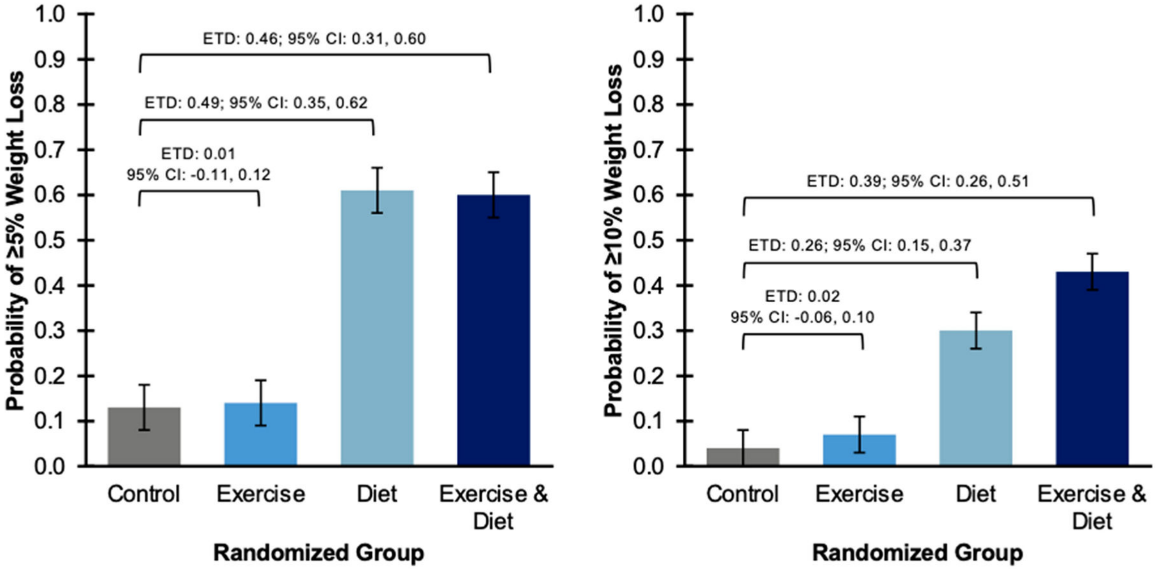

Figure 2.

Proportion of study participants who achieved a weight loss ≥5% (left panel) or ≥10% (right panel) of baseline body weight at week 52 by randomized group

Note: Unobserved data were multiply imputed using a parametric logistic regression imputation method and analyzed using generalized linear model that was adjusted for randomization stratification factors including age, receipt of radiotherapy, number of lymph nodes resected, lymphedema severity, and body mass index. ETD, Estimated Treatment Difference; CI, Confidence Interval.

Table 1.

Baseline characteristics by randomized group

Characteristic	Control (n=90)	Exercise (n=87)	Diet (n=87)	Exercise & Diet (n=87)
Age, y	59.0 (8.5)	59.1 (8.1)	59.4 (9.2)	60.0 (9.0)
Race, n (%)				
White	66 (73.3%)	50 (57.5%)	52 (59.8%)	50 (57.5%)
Black	22 (24.4%)	36 (41.4%)	32 (36.8%)	32 (36.8%)
Other	2 (2.2%)	1 (1.1%)	3 (3.3%)	5 (5.8%)
Education, n (%)				
High school or less	19 (21.1%)	15 (17.2%)	12 (13.8%)	18 (20.7%)
Some college	28 (31.1%)	29 (33.3%)	36 (41.4%)	29 (33.3%)
College degree or more	43 (47.8%)	43 (49.4%)	39 (44.9%)	40 (46.0%)
Time since cancer diagnosis, mo.	97.5 (61.3)	92.6 (64.3)	89.9 (66.9)	87.8 (61.7)
Cancer stage, n (%)				
Ductal carcinoma in situ	10 (11.1%)	6 (6.9%)	5 (5.8%)	3 (3.4%)
I	19 (21.1%)	24 (27.6%)	17 (19.5%)	14 (16.0%)
II	23 (25.6%)	24 (27.6%)	29 (33.3%)	28 (32.2%)
III	16 (17.8%)	13 (14.9%)	20 (23.0%)	21 (24.1%)
Unknown	22 (24.4%)	20 (23.0%)	16 (18.4%)	21 (24.1%)
No. of nodes removed, n	12.7 (9.5)	12.6 (9.4)	12.5 (9.8)	12.0 (8.3)
Cancer treatments, n (%)				
Chemotherapy	74 (82.2%)	65 (74.7%)	71 (81.6%)	79 (90.8%)
Radiotherapy	73 (81.1%)	73 (83.9%)	69 (79.3%)	73 (83.9%)
Tamoxifen	10 (11.1%)	10 (11.5%)	10 (11.5%)	6 (6.9%)
Aromatase inhibitor	31 (34.4%)	25 (28.7%)	22 (25.3%)	24 (27.6%)
Arm volume difference, %	9.6 (14.4)	8.8 (16.6)	8.7 (13.5)	7.6 (13.7)
Body mass index, kg/m^2	34.0 (5.7)	34.0 (6.2)	33.8 (5.6)	34.2 (6.3)
25.0–29.9 kg/m^2	26 (28.9%)	31 (35.6%)	26 (29.9%)	25 (28.7%)
30.0–34.9 kg/m^2	30 (33.3%)	21 (24.1%)	24 (27.6%)	27 (31.0%)
≥35.0 kg/m^2	34 (37.8%)	35 (40.2%)	37 (42.5%)	35 (40.2%)

Values are mean ± standard deviation or n (%). Percentages may not sum to 100.0% due to rounding error.

Table 2.

Change in body composition by randomized group

Endpoint	Randomized Group	Baseline Mean (SD)	52 Week Mean Change (SE)	Estimated Treatment Difference (95% CI)
Body weight, kg	Control	89.3 (16.9)	−0.27 (0.63)	0.00—Reference
	Exercise	89.7 (16.2)	−0.33 (0.66)	−0.06 (−1.85, 1.72)
	Diet	89.9 (16.5)	−5.66 (0.69)[a]	−5.39 (−7.24, −3.55)[b]
	Exercise & Diet	91.2 (16.3)	−6.95 (0.67)[a]	−6.68 (−8.46, −4.90)[b]
Fat mass, kg	Control	40.9 (10.7)	−0.94 (0.51)	0.00—Reference
	Exercise	40.3 (10.9)	−0.79 (0.52)	0.14 (−1.30, 1.59)
	Diet	40.6 (10.3)	−4.52 (0.52)[a]	−3.59 (−5.00, −2.17)[b]
	Exercise & Diet	41.7 (10.2)	−5.22 (0.53)[a]	−4.28 (−5.71, −2.84)[b]
Visceral adipose tissue, cm^2	Control	158.6 (57.2)	−6.59 (3.63)	0.00—Reference
	Exercise	164.8 (75.5)	−12.09 (3.90)[a]	−5.50 (−15.73, 4.73)
	Diet	158.2 (62.2)	−27.87 (3.68)[a]	−21.28 (−31.37, −11.19)[b]
	Exercise & Diet	155.0 (69.6)	−26.46 (3.67)[a]	−19.87 (−30.03, −9.70)[b]
Subcutaneous adipose tissue, cm^2	Control	515.2 (128.0)	−5.05 (7.17)	0.00—Reference
	Exercise	491.9 (133.2)	2.64 (7.16)	7.69 (−12.20, 27.58)
	Diet	507.2 (125.9)	−44.59 (7.40)[a]	−39.53 (−59.85, −19.23)[b]
	Exercise & Diet	502.7 (136.1)	−50.24 (7.46)[a]	−45.19 (−65.14, −25.23)[b]
Lean mass, kg	Control	49.1 (7.6)	−0.06 (0.25)	0.00—Reference
	Exercise	50.1 (6.6)	0.36 (0.25)	0.42 (−0.25, 1.10)
	Diet	49.9 (7.3)	−0.88 (0.24)[a]	−0.82 (−1.50, −0.15)[b]
	Exercise & Diet	50.4 (7.3)	−1.30 (0.24)[a]	−1.24 (−1.92, −0.56)[b]
Appendicular lean mass, kg	Control	21.4 (3.8)	−0.05 (0.11)	0.00—Reference
	Exercise	22.2 (3.7)	0.18 (0.11)	0.23 (−0.08, 0.54)
	Diet	22.0 (3.8)	−0.37 (0.11)[a]	−0.32 (−0.63, −0.01)[b]
	Exercise & Diet	22.3 (3.8)	−0.51 (0.11)[a]	−0.46 (−0.77, −0.15)[b]
Bone mineral density, g/cm^2	Control	1.12 (0.12)	−0.007 (0.004)	0.000—Reference
	Exercise	1.12 (0.13)	−0.007 (0.004)	−0.001 (−0.012, 0.010)
	Diet	1.16 (0.13)	−0.002 (0.004)	0.005 (−0.006, 0.016)
	Exercise & Diet	1.15 (0.14)	−0.003 (0.004)	0.003 (−0.008, 0.014)

Note: Unobserved data were multiply imputed using predictive mean matching and analyzed using a repeated measures analysis of covariance model. Models are adjusted for the baseline value of the dependent variable, and randomization stratification factors including age, receipt of radiotherapy, number of lymph nodes resected, lymphedema severity, and body mass index.

[a]P<0.05 (two-sided) compared with baseline (within group).

[b]P<0.05 (two-sided) compared with control, adjusted for multiplicity.