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CLINICAL TRIAL

Quality of life outcomes from the Exercise and Nutrition Enhance Recovery and Good Health for You (ENERGY)-randomized weight loss trial among breast cancer survivors

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Abstract Obesity is a poor prognostic factor and is negatively related to quality of life (QOL) in breast cancer survivors. Exercise and Nutrition to Enhance Recovery and Good Health for You is the largest weight loss trial completed among cancer survivors. Percent losses in body weight with an intensive group-based intervention versus an attention control were 6.0 versus 1.5 % ($p < 0.0001$) and 3.7 versus 1.3 % ($p < 0.0001$) at 12 and 24 months, respectively. ENERGY also was designed to answer the research question: Does weight loss significantly improve vitality and physical function (key components of QOL)? 692 breast cancer survivors (BMI: 25–45 kg/m^2) at 4 US sites were randomized to a year-long intensive intervention of 52 group sessions and telephone counseling contacts versus a non-intensive (control) of two in-person counseling sessions. Weight, self-reported QOL, and symptoms were measured semi-annually for two years. Significant decreases in physical function and increases in symptoms were observed among controls from baseline to 6 months, but not in the intervention arm, −3.45 (95 % Confidence Interval [CI] −6.10, −0.79, $p = 0.0109$) and 0.10 (95 %CI 0.04, 0.16, $p = 0.0021$), respectively. Improvements in vitality were seen in both arms but trended toward greater improvement in the intervention arm −2.72 (95 % CI −5.45, 0.01, $p = 0.0508$). These differences diminished over time; however, depressive symptoms increased in the intervention versus control arms and became significant at 24 months, −1.64 (95 % CI −3.13, −0.15, $p = 0.0308$). Increased QOL has been reported in shorter term diet and exercise trials among cancer survivors. These longer term data suggest that diet and exercise interventions improve some aspects of QOL, but these benefits may diminish over time.

On behalf of ENERGY Trial Group. The members of ENERGY Trial Group are given in Appendix.

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Introduction

In November 2014, the American Society of Clinical Oncology (ASCO) issued a position statement on obesity and cancer, encouraging oncologists to initiate an open dialog with their patients regarding the importance of weight management [1]. In addition to the prevention of comorbidity and potentially enhanced cancer control, improved quality of life (QOL) was provided as one of the potential benefits of successful weight management.

Previous studies have found that obesity is significantly associated with poorer health-related QOL, especially in women [2]. In an observational study of 661 stage 0-IIIA breast cancer survivors, Imayama et al. [3] found that compared to normal weight survivors (BMI < 25 kg/m^2), those who were obese (BMI ≥ 30 kg/m^2) had significantly lower physical component scores (42.0 vs. 38.5; $p < 0.0001$) and significantly more cancer-related symptoms, such as arm involvement ($p = 0.04$), urinary incontinence ($p = 0.001$), and a tendency to nap ($p = 0.04$). Moreover, those who lost versus gained weight reported significant increases in physical functioning ($p = 0.03$) and decreases in chest wall ($p = 0.01$) and arm symptoms ($p = 0.02$). In a randomized controlled trial (RCT) entitled RENEW (Reach-out to Enhance Wellness) which promoted increased physical activity, a healthy diet, and a slow rate of weight loss among 641 older (age 65+), overweight and obese long-term cancer survivors, of which 45 % ($n = 289$) had been diagnosed with breast cancer, Morey et al. [4] found that at 12-month follow-up, mean physical function scores declined less rapidly in the intervention arm (-2.15; 95 % confidence interval [CI], -0.36 to -3.93) compared with the control arm (-4.84; 95 % CI, -3.04 to -6.63) ($p = 0.03$). Moreover, changes in the intervention arm were significantly more favorable in terms of lessened pain and enhanced vitality, overall health, social functioning, mental health, and physical and emotional roles.

Breast cancer survivors face several challenges to QOL, due in large part to the stresses of uncertainty surrounding a diagnosis of cancer and to adverse effects of adjuvant endocrine therapy and chemotherapy. Compounding these problems is concern over excess adiposity and weight gain during treatment and its impact on body image [5]. The Exercise and Nutrition to Enhance Recovery and Good health for You (ENERGY) trial enrolled 692 overweight or obese breast cancer survivors with dual aims of determining whether significant weight loss could be achieved and sustained over a two-year period in this target population, as well as examining the impact of weight loss on QOL, with the specific hypothesis that weight loss would result in significantly improved vitality and physical functioning [6]. Data on weight loss were published in a recent report and indicate that at 12 months, mean weight losses were 6.0 % of initial weight in the intervention and 1.5 % in the control groups ($p < 0.0001$), and at 24 months, mean weight losses in the intervention and control groups were 3.7 and 1.3 %, respectively ($p < 0.0001$) [7]. The purpose of this analysis was to examine the changes in vitality and physical functioning (the two primary QOL endpoints) by arm assignment; in addition, breast cancer symptoms and depressive symptoms were also explored as secondary outcomes.

Methods

Study design, participants, and randomization

A complete description of ENERGY's research methods has been published previously (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3593786) [6]. In brief, ENERGY was a single-blinded, randomized phase 3 trial conducted at four US sites (San Diego, CA; Denver, CO; St. Louis, MO; and Birmingham, AL). Recruits were women (age 21 + years) with a history of stage I [≥1 cm], II, or III breast cancer diagnosed within the previous 5 years. Enrollees must have completed treatment (exception: endocrine therapy), be overweight or obese [body mass index (BMI) 25-45 kg/m^2], and able to comply with study procedures. Women were excluded if they had a history of malignancies other than breast cancer and non-melanoma skin cancer, serious psychiatric illness, or any medical condition substantially limiting moderate physical activity (CONSORT diagram—Fig. 1). Randomization was performed by the data analysis center (Washington University in St. Louis); participants were assigned to either the intensive intervention (group-based, semi-structured weight loss program supplemented with telephone counseling and tailored newsletters) or the less intensive intervention control arm, stratified by age (<55 years vs. ≥ 55 years), stage (I vs. II and III), and study site. The study was approved and monitored by the Institutional Review Boards of all sites and conformed to the principles of the International Conference on Good Clinical Practice. All participants provided written informed consent.

Interventions

All women received written materials and were counseled to reduce their weight and adhere to dietary and physical activity guidelines of the American Cancer Society; [8]

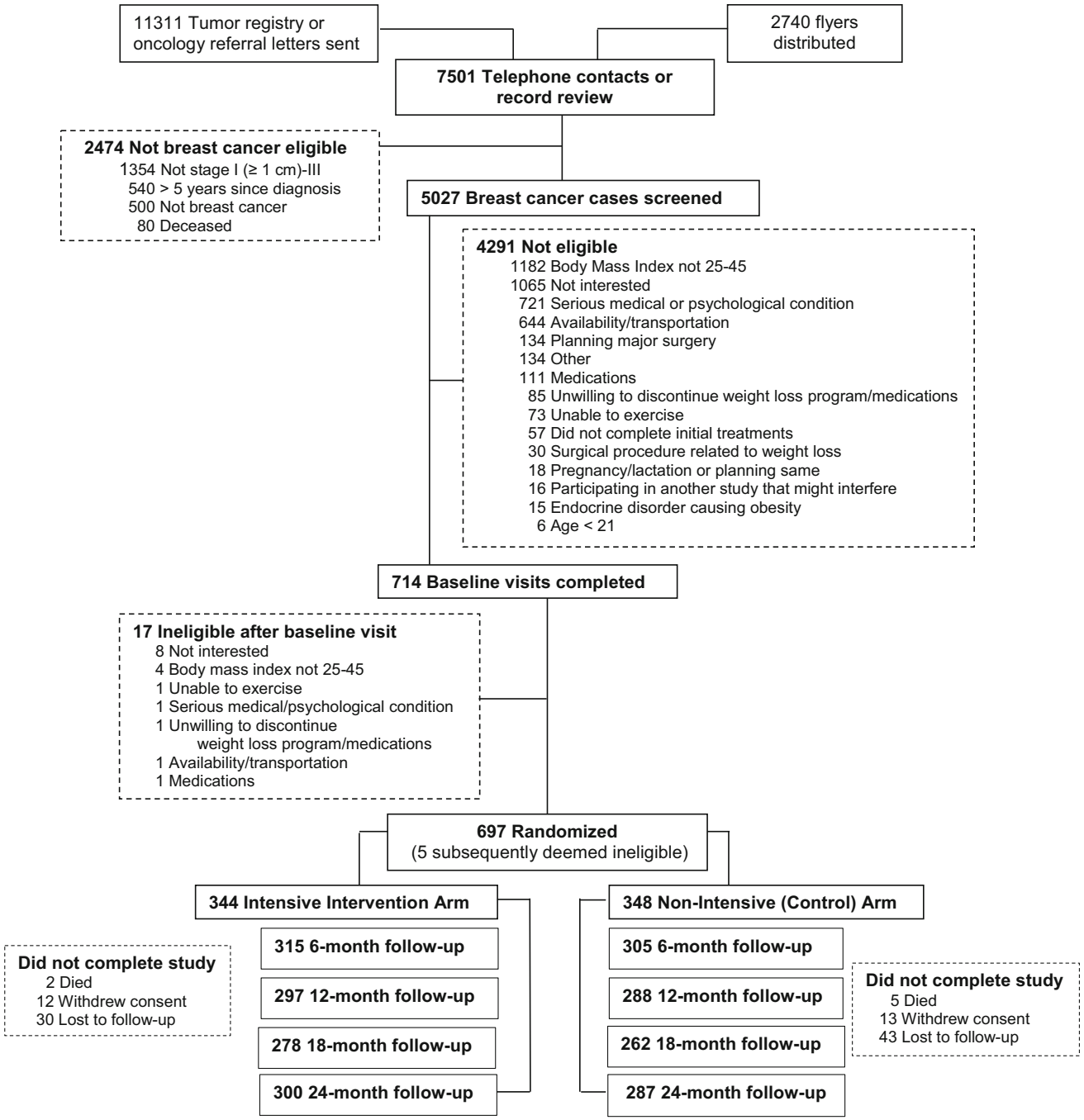

Fig. 1 ENERGY CONSORT diagram for quality of life outcomes

however, one arm received an intensive program to accomplish these goals consisting of four months of weekly one-hour group sessions tapering to fortnightly for 2 months and then monthly from 6 months to 1 year, as well as personalized guidance delivered via telephone and/or email in between each of these group sessions. Mailed newsletters provided additional support on a quarterly basis from 6 to 24 months and were individually tailored based on current information about physical activity, dietary intake, weight, and overcoming barriers to regulating energy balance.

In contrast, controls received two contacts—one at baseline and another at six months.

Measures

At baseline, medical record review was performed to obtain data on breast cancer diagnosis and treatment, and

participant's height was measured. Participants also provided information on medication use, comorbidities, and medical history. From baseline until two-year follow-up, weight, fitness, and survey measures were collected every 6 months. Fitness level was assessed by measuring recovery heart rate after a 3-min step test [9]. A modified version of the Godin Leisure-Time Exercise Questionnaire validated previously in cancer research [10] was used to assess weekly minutes of moderate and strenuous physical activity.

Given the study's focus on QOL, a variety of instruments were administered at baseline and at each semi-annual follow-up. The Short Form Health Survey (SF-36) was used as a general measure of QOL [11–14]. This 8-scale profile of functional health and well-being includes specific scales for vitality and physical functioning, and primary outcomes for this trial. The reliability of the SF-36 (Cronbach's $\alpha > 0.85$, reliability coefficient >0.75) and its construct validity have been established [15].

The refined Impact of Cancer Scale (IOCv2) was used to measure the impact of cancer on QOL [16]. Among breast cancer survivors, analyses on the IOCv2 have yielded a factor structure relating IOC items to psychosocial impact domains that exhibit high factor loadings (factor-item correlations of 0.59–0.94) and internal consistency (Cronbach's $\alpha = 0.76$–0.89). The scales consist of a Positive Impact Summary scale with four subscales (Altruism and Empathy, Health Awareness, Meaning of Cancer, and Positive Self-Evaluation), a Negative Impact Summary scale with four subscales (Appearance Concerns, Body Change Concerns, Life Interferences, and Worry), and subscales for Employment and Relationship Concerns. This instrument was administered every 12 months, since rapid changes in these domains were not anticipated, to minimize patient burden.

The Breast Cancer Prevention Trial (BCPT) Symptom Scales were used to measure concurrent and late side effects of medical interventions to prevent and treat breast cancer [17]. Factor analysis of the BCPT reveals eight factors corresponding to physical symptoms associated with breast cancer treatment, chemoprevention, menopause, and aging, i.e., hot flashes, nausea, bladder control, musculoskeletal pain, problems concerning cognition, arms and vaginal health, and body image.

Depressive symptoms were assessed using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D); [18] this instrument has demonstrated high internal consistency in both the general population and patient samples. Validity has been established with other self-report measures, correlations with clinical ratings of depression, and by construct validity.

Statistical analysis

Vitality and physical function, as assessed by relevant SF36 subscales, served as primary outcomes with the original accrual target set at 800 with roughly 400 participants per arm. Based on the results of a previous study by Fine et al. [19], this sample size provided 95 % power to detect a between-group difference of 3.3 units at an alpha level of 0.025 (to account for two primary outcomes). Given the time and budgetary constraints of this vanguard study, 87 % of the accrual target was enrolled, i.e., an analytical sample of 692 women (344 in the intervention group and 348 controls); therefore, our power was reduced slightly to 92 %.

Comparability of the study groups was examined using Kruskal–Wallis tests for continuous variables and Chi-square tests for categorical variables. Longitudinal mixed models adjusted for time since diagnosis and receipt of chemotherapy (two factors that significantly influence QOL and which were identified a priori) [20] were used to analyze change over time with an assumption that any missing data were missing at random.

Results

The women accrued for this trial were largely post-menopausal (87.4 %) and had a mean (SEM) age of 56.2 (9.50) years. Twenty-one percent of the sample comprised racial/ethnic minorities, which is representative of the US population of women within this age bracket, [21]. Roughly 3-of-4 had stage I or II breast cancer and took anti-estrogens or aromatase inhibitors. At baseline, 41 % were overweight and the remainder were obese; few (23.1 %) met guidelines for 150 min/week of moderate-to-vigorous physical activity [8]. Almost 20 % of women had CES-D scores ≥16, indicative of risk for depression. As seen in Table 1, no between-arm differences were observed at enrollment [16].

Data on depressive symptoms, overall symptoms, and QOL controlling for receipt of chemotherapy and time from diagnosis are presented in Table 2. While vitality increased in both arms from baseline to 6 months, greater changes that approached statistical significance were observed in the intensive intervention arm; no evidence of arm differences existed at more distal time points (Fig. 2). With regard to physical functioning, the intensive intervention arm sustained their baseline levels, while the control arm experienced decline. These differences were statistically significant at 6 months and of borderline significance at 12 months, and then differences further diminished over time.

Table 1 Characteristics of study participants in ENERGY (Exercise and Nutrition Enhance Recovery and Good Health for You) Weight Loss Randomized Trial among Breast Cancer Survivors

	Control (n = 348)	Intensive intervention (n = 344)	p value*
Age, years (mean [SD])	56.4 (9.53)	56.0 (9.47)	0.77
Post-menopausal at study entry—% (n)	87.9 % (306)	86.9 % (299)	0.69
Years from primary treatment to study entry (mean [SD])	2.18 (1.39)	2.02 (1.38)	0.13
Years from diagnosis to study entry (mean [SD])	2.78 (1.41)	2.62 (1.38)	0.13
Breast cancer stage—% (n)			
I	29.3 % (102)	29.4 % (101)	0.93
II	42.5 % (148)	41.3 % (142)	
III	28.2 % (98)	29.4 % (101)	
Chemotherapy—% (n)	75.3 % (262)	77.0 % (265)	0.59
Anti-estrogen use—% (n)			
None	25.9 % (90)	25.9 % (89)	0.73
Anti-estrogen only	22.4 % (78)	20.1 % (69)	
Aromatase inhibitor	51.7 % (180)	54.1 % (186)	
Comorbidities[†]			
0	39.8 % (135)	35.5 % (119)	0.51
1	34.8 % (118)	37.0 % (124)	
2 or more	25.4 % (86)	27.5 % (92)	
Hospitalizations in the past year—% (n)	25.0 % (87)	25.3 % (87)	0.93
Race/Ethnicity[†]—% (n)			
White, non-Hispanic	81.5 % (282)	77.0 % (265)	0.15
Hispanic	5.8 % (20)	7.6 % (26)	
African-American	10.1 % (35)	10.5 % (36)	
Asian	1.7 % (6)	1.5 % (5)	
Mixed/other	0.9 % (3)	3.5 % (12)	
Education (years)			
High school or less	13.8 % (48)	14.8 % (51)	0.88
More than High School, but not a College Graduate	27.3 % (95)	25.6 % (88)	
College Graduate	28.2 % (98)	26.7 % (92)	
Post graduate degree	30.8 % (107)	32.9 % (113)	
Marital status			
Married/partnered	67.5 % (235)	66.3 % (228)	0.73
Single/separated/divorced/widowed	32.5 % (113)	33.7 % (116)	
Work status[†]—% (n)			
Employed, earned income within last 12 months	69.1 % (224)	71.6 % (222)	0.49
fully retired from paid employment	30.9 % (100)	28.4 % (88)	
Currently smoking[†]—% (n)	3.8 % (13)	3.2 % (11)	0.69
Weight at study entry, kg (mean [SD])	83.8 (13.61)	84.1 (14.18)	0.89
Body mass index (kg/m^2)			
25–29.9—% (n)	40.5 % (141)	42.2 % (145)	0.20
30–34.9—% (n)	38.2 % (133)	32.3 % (111)	
35–45.0—% (n)	21.3 % (74)	25.6 % (88)	
Hours Mod-to-Vigorous Physical Activity/wk—Mean (SD)	1.7 (2.34)	1.5 (2.07)	0.79
Fitness—# steps over 3 min—Mean (SD)	56.3 (9.76)	56.9 (10.60)	0.76
SF-36 Vitality Subscale Score—Mean (SD)	58.7 (19.69)	58.7 (21.35)	0.74
SF-36 Physical Function Subscale Score—Mean (SD)	79.0 (18.38)	80.2 (18.67)	0.21
Impact of Cancer Positive Impact Score—Mean (SD)	3.8 (0.56)	3.8 (0.57)	0.20
Impact of Cancer Negative Impact Score—Mean (SD)	2.7 (0.73)	2.7 (0.72)	0.91

Table 1 continued

	Control (n = 348)	Intensive intervention (n = 344)	p value*
Breast Cancer Prevention Trial Symptom—Mean (SD)	2.1 (0.55)	2.0 (0.54)	0.39
Depressive Symptoms (CES-D)—Mean (SD)	10.4 (6.96)	10.7 (7.23)	0.81

* 2-sided Kruskal–Wallis test and the chi-square test, respectively

† The denominator for the percentages is the sum of patients across all categories per group, excluding missing values

Table 2 Main Effects of the ENERGY intervention on quality of life, breast cancer symptoms and risk of depression*

Outcome	Baseline Mean (SEM) (n = 692)	6 M Mean (SEM) (n = 574)	12 M Mean (SEM) (n = 513)	24 M Mean (SEM) (n = 506)	Estimate of intervention on baseline to 12 M Δ (95 % CI)	Estimate of intervention on baseline to 2 M Δ (95 % CI)
SF vitality subscale score						
Intervention	60.5 (1.36)	65.1 (1.20)	62.2 (1.25)	60.5 (1.28)		
Control	60.5 (1.37)	62.4 (1.23)	61.0 (1.29)	63.2 (1.31)		
p value	–	0.0508	0.5092	0.1854	−1.20 (−4.75, 2.36)	2.70 (−1.30, 6.69)
SF-36 physical function						
Subscale score						
Intervention	82.9 (1.31)	82.9 (1.16)	82.0 (1.20)	79.9 (1.24)		
Control	81.9 (1.32)	78.4 (1.18)	77.6 (1.24)	77.9 (1.26)		
p value	–	0.0109	0.0512	0.6214	−3.43 (−6.87, 0.02)	−0.97 (−4.83, 2.89)
Positive impact of cancer						
Score						
Intervention	3.8 (0.03)	–	3.9 (0.03)	3.9 (0.04)		
Control	3.7 (0.04)		3.8 (0.03)	3.8 (0.04)		
p value	–		0.0467	0.2325	−0.07 (−0.14, −0.001)	−0.05 (−0.14, 0.03)
Negative impact of cancer						
Score						
Intervention	2.6 (0.05)		2.5 (0.04)	2.5 (0.05)		
Control	2.6 (0.05)		2.6 (0.05)	2.5 (0.05)		
p value	–		0.2984	0.7709	0.05 (−0.04, 0.13)	−0.02 (−0.13, 0.10)
BCPT symptom score						
Intervention	1.99 (0.03)	1.89 (0.03)	2.01 (0.03)	1.99 (0.03)		
Control	2.02 (0.03)	2.02 (0.03)	2.07 (0.03)	2.02 (0.03)		
p value	–	0.0021	0.4167	0.9179	0.03 (−0.05, 0.12)	−0.005 (−0.099, 0.089)
CES-D						
Intervention	9.9 (0.50)	11.4 (0.44)	11.9 (0.45)	11.8 (0.47)		
Control	9.7 (0.50)	10.6 (0.44)	10.9 (0.47)	9.9 (0.47)		
p value	–	0.3058	0.2480	0.0308	−0.79 (−2.14, 0.55)	−1.64 (−3.13, −0.15)

* Controlled for time from diagnosis and receipt of chemotherapy

No between-arm differences were noted for Negative Impact of Cancer. However, for Positive Impact of Cancer, between-arm differences were observed at 12, but not at 24 months. Transitory improvements in symptoms also were observed in BCPT scores in the intensive intervention arm at 6 months as compared to the control arm, but again these differences diminished over time. Within the BCPT, changes with regard to the body image subscale were particularly noteworthy and improved significantly with the intervention as compared to the control at both 6 months ($p < 0.0001$) and 12 months ($p = 0033$), but differences were not detected at 24 months. In contrast to other data, depressive symptoms increased over time in the intensive intervention as compared to the control arm, and between-group differences reached statistical significance at 24 months.

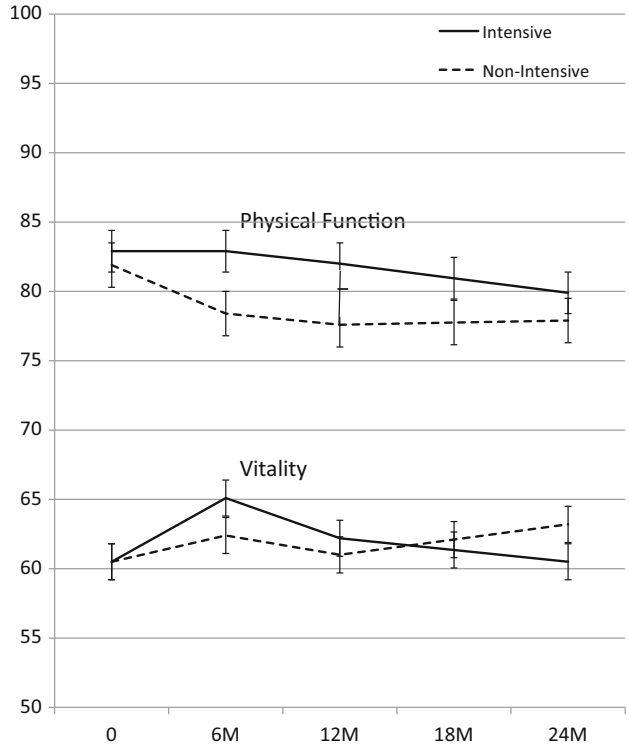

Fig. 2 Change in vitality and physical function over the 24-month study period. For vitality, differences between arms reach borderline significance ($p = 0.0508$) at 6 months but are non-significant at all other time points. For physical function, differences between arms are significant at 6 months ($p = 0.0109$), of borderline significance at 12 months ($p = 0.0512$), and non-significant at all other time points

Several significant correlations were found between changes in these QOL parameters and changes in body weight and physical activity at both 12- and 24-month time points, though correlation coefficients were relatively modest and ranged from −0.09 to −0.27 for body weight and 0.09–0.22 for physical activity (see appendix table). Fitness, as measured by recovery time, appeared consistently and modestly correlated with Positive Impact of Cancer scores, with coefficients, ranging from −0.13 to −0.16.

Discussion

Roughly two-dozen weight loss trials have been conducted in cancer survivors, with the clear majority of these (16, including this study), targeting breast cancer survivors. Similar outcome measures have been reported, but mixed findings have been reported for QOL [22, 23], symptom burden [22], and depressive symptomatology [22]. Results of the ENERGY trial make an important contribution to this area of research as it is the largest weight loss trial reported in cancer survivors and clearly exceeds the size of all weight loss trials conducted in cancer survivors to date.

Similar to the findings of the RENEW trial [4], and the more recently completed Lifestyle Intervention in Adjuvant Treatment of Early Breast Cancer (LISA) Study that was conducted in 338 breast cancer patients who were currently receiving letrozole and randomized to either an intensive telephone-based intervention vs. metformin or placebo groups [23], we saw improvements with our intensive behavioral intervention arm in physical function and vitality. In addition, similar to the RENEW trial [24], we also found that changes in body weight were directly associated with changes in physical function. However, in the ENERGY trial, differences in vitality were not as strong and only reached borderline significance; moreover, between-arm differences in these QOL components diminished more rapidly over time, rather than being largely sustained over the two-year study period. Indeed, there are few lifestyle intervention trials that address long-term changes in behavior and outcomes, with ENERGY, LISA, and RENEW providing the only data in this arena. This relative dearth of long-term data was commented upon in a recent systematic review and meta-analysis of studies that have tested physical activity interventions (one component of energy balance) among cancer survivors, in which standardized mean differences (SMD) of 0.46 (95 % CI 0.09, 0.84) and 0.40 (95 % CI −2.72, 3.52) were detected in global quality of life and vitality, respectively [25]. However, it was noted that the majority of these trials were at most 6 months in duration and were associated with a high degree of bias.

Our results that the intensive intervention arm reported a significant decrease in BCPT symptoms over the first 6 months of the study period, as compared to stable levels in the control arm, parallel those of Befort et al. [26]. In their single-arm, 6-month study of 34 breast cancer survivors, they also found significant improvements in body image, as well as significantly less depression. Unlike the results of Befort et al. [26], we did not find a decrease, but rather a significant increase in depressive symptomatology over time in our intensive weight loss arm.

Our data on depression mirror those of other studies of depression and weight loss that have been reported in the general population over the past two decades [27–29], where three phenomena have been documented consistently: (1) depressed individuals do not lose as much weight in weight loss programs; (2) among those who are depressed, more rapid weight loss is associated with worsening (not improving) depression scores; and (3) relapse (weight regain) occurs most often in those who are most depressed. A classic paper from Brownell and colleagues offers explanations as to why these phenomena

occur, and centers around the social aspects of food, eating, and the rewards that it provides [27]. Given the centrality of food in our culture, it is not uncommon for individuals on weight loss programs to begin to feel socially isolated, as well as torn from their prior food-based coping strategies. While the intensive intervention ENERGY sessions addressed these issues and suggested alternate avenues for social interaction, it may not have been sufficient or sustained for a long enough period of time. In particular, it is noteworthy that the improvements observed in QOL dissipated and depression became more significant as the frequency of group classes (and hence social support) diminished. To our knowledge, there are no other studies which have reported this finding; therefore, it is unknown if these data generalize to other populations or are specific to breast cancer survivors who elect to participate in a group-based intervention and consequently seeking increased interactions with others.

Finally, while a statistically significant between-arm difference in the Positive Impact of Cancer was detected at 12 months, we hesitate to make too much of these results. For this measure, a slight increase in score of 0.1 points was reported in both study arms and likely could be the result of multiple testing, which is a limitation of our exploratory analyses of secondary endpoints.

In summary, results from this large RCT in a diverse and representative sample of overweight and obese breast cancer survivors showed that while the intensive, group-based intervention was effective in promoting weight loss, only borderline increases in vitality and transitory improvements in physical functioning and symptoms resulted. The intensive intervention also was associated with increasing depressive symptomatology. Thus, in many ways, data from the ENERGY trial corroborate the variable impact that weight loss interventions have on QOL and psychosocial endpoints. These findings also shed light on the effects of recidivism that occurs with weight loss interventions in this important patient population and supports the need for future research that can effectively triage patients to programs that address their particular needs. More research is needed to develop programs that effectively promote weight loss and maintenance in substantial sub-populations of survivors who may need additional support or other interventions.

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Author contributors The primary data were made available to the investigators for independent central review and analyses. JL performed the statistical analyses. WDW wrote the first draft of the manuscript, with review and revision by the other authors. All authors had full access to all the data in the study, made the decision to submit these data for publication, were involved in writing the manuscript and agreed on the final content of the manuscript.

Compliance with ethical standards

Conflict of interests All authors declare no competing interests, with the only exception being Dr. Wolin who reports equity from Scale Down LLC and Coeus Health LLC, personal fees from Takeda, and a pending patent for weight management software.

Appendix: The ENERGY Trial Group

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University of Alabama at Birmingham: Wendy Demark-Wahnefried, Ph.D, RD, Helen Krontiras, MD, Maria Azrad, Ph.D, RD, Cindy Blair, Ph.D, Lahnor Powell, DO, and Laura Lee Goree, MS, RD.

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