Weight Loss Interventions for Breast Cancer Survivors: Impact of Dietary Pattern

Henry J. Thompson1 *, Scot M. Sedlacek1,2, Mary C. Playdon1, Pamela Wolfe3, John N. McGinley1, Devchand Paul2, Susan G. Lakoski4

1 Cancer Prevention Laboratory, Colorado State University, Fort Collins, Colorado, United States of America, 2 Rocky Mountain Cancer Centers, Denver, Colorado, United States of America, 3 Colorado Biostatistics Consortium, University of Colorado Denver, Colorado, United States of America, 4 Department of Internal Medicine, University of Vermont, Burlington, Vermont, United States of America

* henry.thompson@colostate.edu

Abstract

Body weight management is not emphasized in clinical practice guidelines for breast cancer survivors, reflecting the lack of evidence that weight loss improves prognosis. Even if this situation changes, the optimal design for weight loss interventions is unclear. We conducted a 6-month non-randomized, controlled weight loss intervention in 249 post-menopausal breast cancer survivors. This paper reports effects on two secondary endpoints, change in body weight and composition. Participants were predominantly non-Hispanic whites (89%) with a mean age of 54.9 ± 9.2 years, a mean BMI of 29.0 ± 2.6 kg/m² and an average of 43 ± 5% body fat. Two dietary interventions, low fat or low carbohydrate, were investigated and consisted of a 42 day cycle of menus and recipes. Weight loss counseling and anthropometric assessment were provided at monthly clinic visits. One hundred ninety-two women completed the trial (77% retention). In comparison to the nonintervention control, both intervention arms achieved significant decreases in body weight (12.5%), body fat (27.5%), waist circumference (9.5%), and hip circumference (7.8%) (all \( p < 0.001 \)) with minimal effects on lean mass (1.3% decrease). Median time to 5 and 10% weight loss was 2 (95% confidence interval = 1 to 3) and 4 (95% confidence interval = 3 to 5) months, respectively, and 23% of participants experienced ≥ 15% weight loss. Loss of body weight and fat mass was rapid and substantial irrespective of dietary approach when a structured program was provided with monthly anthropometric assessment and weight loss counseling.

Trial Registration

ClinicalTrials.gov NCT01315483

Introduction

Overweight and obesity, which are associated with excessive and abnormal accumulation of body fat, have been reported to worsen prognosis for long term survival following treatment for breast cancer [1]. Available evidence indicates that poorer prognosis is observed when
incident cancer occurs in either pre- or post-menopausal overweight or obese women compared to normal weight. The prognostic disadvantage is accounted for by a higher risk of recurrence with subsequent metastatic progression and by the occurrence of cardiovascular disease and type-2 diabetes [2], common co-morbidities of breast cancer survivors. Because the evidence that weight loss improves prognosis is currently considered inadequate [2,3], concern has been expressed in the medical community that giving survivors the task of losing weight represents an unwarranted burden [4]. Thus, body weight management is not emphasized in recently updated clinical practice guidelines despite the fact that the American Society of Clinical Oncology advocates education, awareness, practitioner support, and policy-level change for addressing obesity in the context of cancer prevention and survival [5,6].

The cornerstone of therapeutic interventions to treat or prevent obesity-associated diseases is weight loss via lifestyle modifications involving energy intake and expenditure [7,8]. A number of randomized control trials (RCTs) have been conducted to evaluate various approaches to weight loss and specific dietary patterns have been assessed [9–11]. However, the number of intervention studies of weight loss in breast cancer survivors is still small [12], and as noted in [13], limited sample sizes and short duration of follow-up limit the ability to draw conclusions regarding the most efficacious weight-loss intervention after a breast cancer diagnosis. Moreover, there is little evidence that weight loss programs have been specifically designed for breast cancer survivors, most of whom are considered post-menopausal following completion of treatment [13]. This provided the rationale for focusing on post-menopausal breast cancer survivors in this study and for designing menu plans based on the feedback of breast cancer survivors who participated in a pilot study (Unpublished, HJT).

Many dietary approaches to weight loss have been evaluated in various populations [9,14]. Those that have received the most attention are dietary patterns that are either low carbohydrate or low fat when the macronutrient composition of the diet is expressed as a percent of dietary energy. While interest in macronutrient composition of the diet during weight loss has centered on whether greater weight loss and reduction in percent body fat occurs with diets low in fat versus carbohydrate, the results of a number of RCTs have concluded that these dietary patterns have equivalent effects [9,15]. However, relative to cancer prognosis, emerging but controversial evidence indicates that high glycemic load dietary patterns may increase breast cancer risk [16–22], thus making the comparison of dietary pattern important to investigate in the context of cancer survivorship.

The purpose of this paper is to report on magnitude of weight loss and differences in body composition, both designated secondary endpoints [23], which occurred in breast cancer survivors who followed a 6-month, low fat or low carbohydrate weight loss dietary plan. This study is referred to as CHOICE. The primary endpoint of CHOICE was to determine how weight loss and dietary pattern affect prognostic biomarkers for long-term survival and those findings will be reported separately. Unlike other studies of this type, a 6-week meal plan that was menu- and recipe-defined was provided to each participant. Participants chose from these menus interchangeable, macronutrient-defined (as % energy) and calorie-controlled meals over the 6-month duration of the study. The expectation was that this approach would increase adherence to specific dietary patterns assessed via daily food logs. Moreover, unlike other weight loss studies, anthropometric data were collected monthly, permitting regular adjustment of energy intake and expenditure goals. Monthly clinical visits also reinforced participant accountability for achieving a targeted weight loss objective. A non-randomized design was adopted given concerns that the use of an RCT in dietary interventions may bias potential differences between dietary groups toward the null [24,25]. We judged this particularly important because randomization by dietary pattern may conflict with strong personal dietary preferences, an issue that could be exacerbated in individuals who have undergone cancer therapy.
Materials and Methods

Study Design and Participants

The protocol for this trial and supporting CONSORT checklist are available as supporting information; see S1 CONSORT Checklist and S1 Protocol. This study, referred to as CHOICE, was a 6-month non-randomized controlled trial that compared two weight loss interventions, low carbohydrate or low fat, to a nonintervention control. The clinical protocol for CHOICE was described in [23] and the effects of dietary pattern and weight loss on plasma biomarkers of lipid metabolism, which were measured monthly as part of safety monitoring, have also been reported [26]. Potentially eligible women were referred to the research team by their attending physician during a normally scheduled clinical visit and those women who met eligibility criteria were offered participation in the study. Women who enrolled were followed for 6 months in order to create the opportunity for them to achieve a BMI within the normal range and recognizing that weight loss compliance usually decreases for longer periods of time. Anthropometric data (body weight, waist and hip circumference, body mass index, and body composition) were measured monthly. Accrual occurred from 2008 to 2012.

The details of the CHOICE research protocol including eligibility criteria have been published [23]. Briefly, to be eligible, participants were referred by their clinical oncologist, had a pathology report confirming the resected stage of breast cancer and documentation of the type of systemic adjuvant therapy, and had a BMI in the overweight or obese class I range (BMI 25–34.9 kg/m²). In addition, participants: did not anticipate surgery over the study duration period; did not follow a special diet excluding foods or food groups; had not lost 4 or more pounds of body weight over the month preceding study initiation; did not take pharmaceuticals or supplements for weight management; were not being treated for diabetes or blood glucose control; had no history of eating disorders; did not have digestive issues that might interfere with dietary intake, such as irritable bowel syndrome, Crohn’s, or diverticulitis; never had surgery involving constriction or removal of any portion of the gastrointestinal tract; did not have implanted electronic devices such as a pacemaker; and did not use tobacco products. Participants also had to be willing to follow a dietary plan prescribed for the duration of the study; and adhere to American Cancer Society alcohol guidelines (≤1 standard drink per day). Participants were asked to attend 10 one-on-one clinic visits and 5 group visits over 27 weeks and provide 7 fasting blood samples and 3-day pooled urine samples. Enrollment was initiated in 2008 and completed in 2012. Based on work on the primary endpoint, C-reactive protein, published in 2009 [27], and as necessitated by repeated budgetary reductions by the funding agency throughout the clinical trial, statistical power was recomputed for a different end point and the sample size for each group was reduced. This accounts for the lower levels of enrollment relative to those proposed in [23].

Ethics Statement

The clinical protocol was approved by the Colorado State University Institutional Review Board for the Protection of Human Subjects. Written consent was obtained before enrolling participants.

Non Intervention Control

Eligible women not interested in participating in the weight loss intervention arms were given the opportunity to enroll in the non-intervention control group. This group was given information about the importance of avoiding post treatment weight gain and the health benefits of
having a body mass index in the normal range. Anthropometric data were only collected at baseline and end of study.

**Intervention Designed for Breast Cancer Survivors**

Two interventions were designed based on input from participants of a pilot study of weight loss in breast cancer survivors conducted in the same clinical practice in which the intervention was conducted, one year before the intervention study was initiated. That study (Unpublished, HJT) indicated: 1) that a structured diet plan was beneficial to maintaining accountability in losing weight, 2) that the opportunity to evaluate a dietary plan for feasible adaptation to an individual’s taste preferences, which can be altered by cancer treatment, was critical to making a commitment to a program of weight loss, 3) that while a structured weight loss program was critical to reduce cognitive stress, it needed flexibility for life style adaptation and to match culinary abilities, and 4) that many survivors were unable or unwilling to exercise but that increasing activity by walking was highly acceptable. Accordingly, two interventions were developed and were comprised of a structured diet and physical activity program designed to create a weekly negative energy balance equivalent to 3500 kcal, after adjustments for metabolic adaptations that occur during extended periods of weight loss. The intervention groups received the same physical activity protocol promoting 10,000 steps per day and one of two diets that reflect commonly used weight loss approaches that were identified in our pilot study as being of greatest interest to the survivor population. The dietary patterns investigated contained a low percentage of dietary energy as either fat or carbohydrate.

The diet plan for each intervention arm was comprised of a 42-day cycle of menus and recipes. The recipes for each day’s diet plan were entered into ProNutra Diet Analysis software (Version 3.3.0.10, Viocare, Inc., Princeton, NJ) to assure that all breakfast, lunch, or dinner menus had the same percent of dietary energy from protein, fat, and carbohydrate and were therefore interchangeable in this regard. The 42-day cycle menus were designed for five calorie levels in each intervention arm. The meal plans included interchangeable meal options (home-prepared recipes and meal instructions; eating out and convenience meal options), educational material and a program incorporating weight loss strategies. The intervention was designed as a feeding study but was conducted in free living individuals, where strict dietary structure is presented in a format that also offers enough flexibility to be adopted into daily living. To accommodate the importance that survivors in our pilot study placed on acceptability of a dietary plan, and prior to beginning the intervention, participants followed menus and recipes for three days of each intervention and discussed their concerns with the study dietitians. Assignment to intervention arm was made by the project staff based on this dialogue. Since many participants did not have a specific dietary preference, the need to maintain balance in resected disease stage and type of treatment between intervention arms was considered in assignment to the intervention arm and it was possible to maintain balance in study arm assignment throughout the 2008–2012 time span over which the intervention was conducted. Adherence was assessed by the study registered dietitians by monthly level of weight loss as well as daily food record.

**Statistical Methods**

Differences in cohort characteristics at baseline across intervention arms and between completers and those lost to follow-up were evaluated using the global F test in a one-way analysis of variance for continuous variables; categorical data were evaluated using a chi-square test for equal proportions. Six-month changes in weight and body composition for each diet group vs control were evaluated in an ANOVA model. For comparing 6-month change between diet
groups, an ANCOVA model was used; covariates were baseline BMI, baseline resting metabolic rate, 6-month change in steps, and elapsed time since the end of treatment. The shape of the response curve for weight loss over time was estimated using a maximum likelihood method for repeated measures to accommodate the first order autocorrelation between visits for an individual; the model included baseline BMI, baseline resting metabolic rate, elapsed time since the end of treatment, and the time varying covariate steps; orthogonal polynomial contrasts were used to estimate the shape of the response curve over time. Sensitivity analysis for between-diet differences in 6-month change was done to assess the effects of limiting the comparison to those who completed the 6-month intervention (n = 139) by including all subjects who provided baseline data (n = 167) and a) coding the missing 6-month weight change as 0 or b) using a traditional LOCF (last observation carried forward) analysis; in both cases when 6-month change in steps was missing we used the last recorded value to compute change from baseline. Time-to-event data were evaluated by Kaplan-Meier plots and Cox proportional hazards models. SAS version 9.3 (SAS Institute Inc., Cary, NC) was used for all statistical analyses. GraphPad Prism 5.0 (GraphPad Software, Inc., La Jolla, CA) was used to visualize the data.

Results

Study Participants

A total of 249 participants were assigned to the study (Fig 1). Clinical characteristics and demographic data across groups at baseline are shown in Table 1. Participants were predominately non-Hispanic whites (89%) with a mean age of 54.9 ± 9.2 years, a mean BMI of 29.0 ± 2.6 kg/
m² and an average of 43 ± 5% body fat. There were no differences across study arms in clinical or demographic characteristics, including disease stage or treatment regime. During the course of the study, dropout rate was similar in the low carbohydrate (15%) and the low fat (18%) study arms, although it was higher in the non-intervention control (26%); the differences were not statistically significant \( (p = 0.22) \). Demographics for the 47 cases lost to follow up were not different from those who completed the study, with the exception of time since end of treatment \( (p = 0.01) \).

### Outcomes

On average the intervention groups lost 9.9 [95% CI = 9.1 to 10.6] kg of body weight, 9.3 [95% CI = 8.6 to 9.9] kg of body fat, 0.6 [95% CI = 0.4 to 0.9] kg of lean weight, 3.7 [95% CI = 3.4 to 3.9] units in body mass index, 8.9 [95% CI = 8.0 to 9.7] cm in waist circumference, and 8.7 [95% CI = 7.9 to 9.5] cm in hip circumference (Table 2). The changes in all parameters, with the exception of lean weight, compared to the changes in the control group were statistically significant \( (p < 0.001) \) in an unadjusted ANOVA model. The differences between the intervention arms in the primary measures, weight loss, fat weight loss, and lean weight maintenance, gradually diverged over six months. Average cumulative weight loss (kg) (Fig 2A), average cumulative fat loss (kg) (Fig 2B) and average cumulative loss of lean mass (kg) (Fig 2C) are shown as a function of time. Progressive loss of body weight and body fat were best described as a curvilinear (quadratic) response \( (p < 0.01) \). The cumulative loss of lean mass was greater in the first 2 months, but there was no evidence for a trend over time. An ANCOVA model controlling for baseline BMI, RMR, elapsed time since end of treatment, and the 6-month change in steps, was used to test for between diet differences in 6-month percent change (Table 3). None of the measures was statistically significant at the six-month visit. Sensitivity analyses that included all 167 participants in the 2 diet interventions and filled missing

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**Table 1. Baseline characteristics.**

| Variable      | Control n = 53 | Low fat n = 73 | Low carbohydrate n = 66 | p-value (Global F) |
|---------------|----------------|----------------|--------------------------|--------------------|
| Race          |                |                |                          |                    |
| White         | 50 (94)        | 70 (96)        | 72 (94)                  | 0.82               |
| Black         | 2 (4)          | 1 (1)          | 3 (4)                    | 0.46               |
| Hispanic      | 1 (2)          | 1 (1)          | 3 (4)                    |                    |
| Other         | 1 (2)          | 2 (3)          | 1 (2)                    |                    |
| Age (years)   | 57.7 ± 7.6     | 54.5 ± 9.2     | 55.2 ± 8.9               | 0.11               |
| Height (cm)   | 164 ± 6        | 166 ± 6        | 165 ± 7                  | 0.48               |
| BMI (kg/m²)   | 29.2 ± 2.7     | 28.2 ± 2.4     | 29.4 ± 2.5               | 0.01               |
| Weight (kg)   | 79.7 ± 9.3     | 77.6 ± 7.7     | 79.7 ± 8.6               | 0.24               |
| Fat Wt (kg)   | 34.9 ± 7.3     | 33.0 ± 5.8     | 35.0 ± 6.0               | 0.11               |
| Fat Mass (%)  | 43.5 ± 5.3     | 42.4 ± 5.2     | 43.8 ± 4.6               | 0.24               |
| Lean Wt (kg)  | 44.8 ± 4.8     | 44.6 ± 5.2     | 44.8 ± 5.1               | 0.97               |
| Lean Mass (%) | 56.5 ± 5.3     | 57.6 ± 5.1     | 56.3 ± 4.6               | 0.24               |
| Waist (cm)    | 95 ± 8         | 92 ± 7         | 94 ± 7                   | 0.03               |
| Hip (cm)      | 111 ± 7        | 111 ± 6        | 112 ± 7                  | 0.40               |
| RMR (kcal/d)  | 1297 ± 132     | 1284 ± 136     | 1296 ± 137               | 0.83               |
| Steps (daily) | 6257 ± 3027    | 7535 ± 2957    | 7096 ± 2989              | 0.08               |

Values are mean ± SD or N (%)

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Table 2. Anthropometric measures and body composition.

| Variable       | Time     | Control (n = 53) | Low fat (n = 73) | Low carbohydrate (n = 66) |
|----------------|----------|------------------|------------------|---------------------------|
| Weight (kg)    | Baseline | 79.7 (77.1 to 82.3) | 77.6 (75.8 to 79.4) | 79.8 (77.6 to 81.9) |
|                | 6 months | 79.4 (76.6 to 82.1) | 68.3 (66.5 to 70.0) | 69.3 (67.1 to 71.5) |
|                | Change   | -0.4 (-1.0 to 0.3) | -9.3 (-10.3 to -8.3) | -10.5 (-11.6 to -9.3) |
| Body Mass Index| Baseline | 29.2 (28.5 to 30.0) | 28.2 (27.6 to 28.8) | 29.4 (28.7 to 30.0) |
|                | 6 months | 29.1 (28.3 to 29.9) | 24.8 (24.2 to 25.3) | 25.5 (24.8 to 26.1) |
|                | Change   | -0.2 (-0.4 to 0.1) | -3.4 (-3.8 to -3.1) | -3.9 (-4.3 to -3.5) |
| Fat weight(kg) | Baseline | 34.9 (32.9 to 36.9) | 33.0 (31.6 to 34.3) | 35.0 (33.5 to 36.5) |
|                | 6 months | 34.9 (32.6 to 37.1) | 24.1 (22.8 to 25.5) | 25.3 (23.7 to 26.9) |
|                | Change   | -0.0 (-0.7 to 0.6) | -8.9 (-9.8 to -7.9) | -9.7 (-10.7 to -8.7) |
| % Fat Mass     | Baseline | 43.5 (42.0 to 44.9) | 42.4 (41.2 to 43.6) | 43.8 (42.6 to 44.9) |
|                | 6 months | 43.5 (41.9 to 45.2) | 35.1 (33.7 to 36.5) | 36.2 (34.7 to 37.7) |
|                | Change   | 0.1 (-0.5 to 0.6)  | -7.3 (-8.1 to -6.4) | -7.6 (-8.5 to -6.7) |
| Lean weight(kg)| Baseline | 44.8 (43.5 to 46.1) | 44.6 (43.4 to 45.8) | 44.8 (43.5 to 46.0) |
|                | 6 months | 44.5 (43.1 to 45.8) | 44.2 (42.9 to 45.4) | 44.0 (42.7 to 45.2) |
|                | Change   | -0.3 (-0.7 to 0.0) | -0.4 (-0.8 to -0.1) | -0.8 (-1.2 to -0.4) |
| % Lean Mass    | Baseline | 56.5 (55.1 to 58.0) | 57.6 (56.4 to 58.8) | 56.3 (55.1 to 57.4) |
|                | 6 months | 56.5 (54.8 to 58.1) | 64.9 (63.5 to 66.3) | 63.8 (62.3 to 65.3) |
|                | Change   | -0.1 (-0.6, 0.5)   | 7.3 (6.4 to 8.1)   | 7.6 (6.7 to 8.5)   |
| Waist (cm)     | Baseline | 94.9 (92.6 to 97.2) | 91.6 (89.9 to 93.3) | 94.2 (92.5 to 95.9) |
|                | 6 months | 94.8 (92.4 to 97.2) | 83.1 (81.3 to 84.8) | 85.0 (83.1 to 86.8) |
|                | Change   | -0.1 (-1.6 to 1.4) | -8.5 (-9.7 to -7.4) | -9.3 (-10.6 to -7.9) |
| Hip (cm)       | Baseline | 110.6 (108.5 to 112.6) | 110.7 (109.4 to 112.1) | 112.0 (110.3 to 113.8) |
|                | 6 months | 111.0 (108.4 to 113.5) | 102.2 (100.9 to 103.5) | 103.1 (101.4 to 104.9) |

(Continued)
outcomes with either the last observation carried forward or 0 where 6-month data were missing also showed no difference between diets.

**Weight Loss**

Box plots were constructed and show the progressive increments in change in percent of initial body weight and the increasing variation in response among individuals over time (Fig 3). Weight loss magnitude at the end of the intervention was 8, 27, 32, 23, and 10%, respectively, for the following categories: <5%, 5.0 to 9.9%, 10.0 to 14.9%, 15.0 to 19.9%, and ≥ 20% weight loss relative to initial weight (Table 4). The differences between intervention arms were not statistically significant.

Kaplan-Meier plots (Fig 4) quantify the time frame over which participants in each intervention arm achieved at least a 5 or 10% reduction in body weight relative to initial body weight. Greater than 90% of all women in both intervention arms achieved at least 5% weight loss with a median time to achieving this goal of 2 months (95% CI = 1 to 3 months, Fig 4A). Change occurred more rapidly in the low carbohydrate intervention arm but the differences were not statistically significant using a Cox regression controlling for baseline BMI, baseline RMR, 6 month change in steps and elapsed time since end of treatment; the model was repeated for time to 5% weight loss (p = 0.52), time to 10% weight loss (p = 0.83), time to 15% weight loss (p = 0.39) and time to 20% weight loss (p = 0.40). Median time to loss of ≥ 10% of initial body weight was 4 months (95% CI = 3 to 5 months, Fig 4B)

**Adverse Events**

The following adverse events were recorded: treated for a pulmonary embolism (1), treated at an emergency room for stomach pain (1), treated for falls (2), one of which resulted in a hairline hip fracture, and allergic reaction to an antibiotic (1). All adverse events were determined
Discussion

The number of breast cancer survivors continues to increase [28]. These women remain at risk for breast cancer recurrence, with survival adversely affected by being overweight or obese [1]. This situation gives urgency to understanding body weight regulation as a potential avenue to improve prognosis [2]. What has been shown in post-menopausal women (not breast cancer survivors) is that limiting caloric intake rather than increasing energy expenditure via physical activity is key to achieving weight loss [29]. In our study, overweight-to-obese postmenopausal breast cancer survivors being routinely followed by a team of medical oncologists working in a private practice setting were remarkably successful in rapid weight loss that was quantified by time-to-event analysis. Weight loss occurred in the absence of adverse events related to the intervention and with little loss of lean mass. The preservation of lean mass is noteworthy and may be due in part to that fact that participants were physically active, although activity levels, measured as daily steps, did not differ between intervention arms. Whether participants were assigned to a low carbohydrate or low fat dietary pattern, average weight loss was 12.5%, which is markedly higher than reported in other studies [13] and only 8% of the study population failed to lose at least 5% of initial body weight, which is a clinically meaningful level of weight loss [30]. This level of success is likely attributed to the fact that the intervention was specifically designed for breast cancer survivors based on their preferences measured during a pilot study. From a clinical practice perspective, the intervention program worked well within the constraints of a large medical oncology practice in the private practice setting (Program details: Table 5).

A curvilinear response was demonstrated in loss of body fat that directly paralleled the loss of body weight (Table 2; Fig 2B). The changes in body fat composition represent a key finding.

### Table 3. Estimates of between group differences in percent change from baseline for weight loss and body composition at the six month visit.

| Between group difference (LC-LF) Mean ± SEM (p-value) | Elapsed | Steps | RMR | BMI |
|-------------------------------------------------|---------|-------|-----|-----|
| % change wt (kg) | CC 0.76 ± 0.91 (0.40) | 0.43 | 0.005 | 0.47 | 0.03 |
|                  | LOCF 0.76 ± 0.92 (0.41) | 0.04 | 0.009 | 0.49 | 0.42 |
|                  | Zero 0.81 ± 1.07 (0.45) | 0.02 | 0.06 | 0.60 | 0.73 |
| % change fat wt (kg) | CC 1.96 ± 1.97 (0.32) | 0.84 | 0.001 | 0.85 | 0.59 |
|                  | LOCF 2.23 ± 1.99 (0.26) | 0.17 | 0.003 | 0.48 | 0.07 |
|                  | Zero 1.99 ± 2.31 (0.39) | 0.05 | 0.04 | 0.56 | 0.10 |
| % change lean wt (kg) | CC 0.23 ± 0.59 (0.69) | 0.60 | 0.62 | 0.68 | 0.18 |
|                  | AAD -0.07 ± 0.52 (0.90) | 0.35 | 0.37 | 0.98 | 0.08 |
|                  | Zero 0.27 ± 0.49 (0.57) | 0.38 | 0.57 | 0.75 | 0.30 |

Abbreviations: CC, complete cases (n = 139); LOCF, last observation carried forward (n = 167); Zero, missing 6-month change set to 0 (n = 167); low fat, LF; low carbohydrate, LC; steps, 6-month change in steps; Elapsed, Elapsed time from completion of treatment to initiation of CHOICE; RMR, baseline resting metabolic rate; BMI, baseline body mass index. Inference was done using an ANCOVA model regressing 6-month change on clinically important variables. Note that the sensitivity analysis is conclusive, regardless of the assumptions about missing data the 6-month changes are not different by diet.

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given the linkages among adiposity, insulin resistance, chronic inflammation, and peripheral aromatization which are metabolic processes implicated not only in breast cancer progression but also in the risk for the common co-morbidities among postmenopausal breast cancer survivors, namely, cardiovascular disease and type-2 diabetes [31]. The changes in waist and hip circumference indicated that fat was being uniformly lost from both peripheral and central fat depots irrespective of the intervention arm to which the participant was assigned.

Despite the success of the current study, there was a broad range in the percent weight loss (Fig 4; Table 4) underscoring the importance of determining whether the magnitude of survival

**Table 4. Weight Loss Success by Intervention Arm.**

| Intervention Arm | < 5.0% | 5 to 9.9% | 10.0 to 14.9% | 15.0 to 19.9% | ≥ 20.0% |
|------------------|--------|-----------|---------------|---------------|--------|
| Low fat          | 6 (8.2%) | 23 (31.5%) | 24 (32.9%)    | 15 (20.6%)    | 5 (6.9%) |
| Low carbohydrate | 5 (7.6%) | 15 (22.7%) | 20 (30.3%)    | 17 (25.8%)    | 9 (13.6%) |

Values are n (% of total). The differences between intervention arms were not statistically significant.

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Fig 4. Time-to-Event Analysis for Weight Loss Success According to Intervention Arm. Kaplan-Meier plots were constructed in order to quantify the time frame over which participants in each intervention arm achieved at least a 5%, or 10% reduction in body weight relative to initial body weight. Each plot shows the percent of women in each arm that achieved at least the stated percent weight loss by month. (A) greater than 90% of all women in both intervention arms achieved at least 5% weight loss with a median time to achieving this goal of 2 months (95% CI = 1 to 3 months). Change occurred more rapidly in the low carbohydrate intervention arm but the differences were not statistically significant, tested using a Cox proportional hazard model controlling for BMI, RMR, steps, and elapsed time from end of treatment. (B) median time to loss of ≥10% of initial body weight was 4 months (95% CI = 3 to 5 months). LC, low carbohydrate. LF, low fat.

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Table 5. Framework for CHOICE as a Transportable Weight Loss Intervention Program.

| Intervention Component          | Resource                  | Description                                                                 |
|--------------------------------|---------------------------|-----------------------------------------------------------------------------|
| Recruitment                     | Brochure                  | Available at front desk reception and medical examination rooms              |
|                                | Flyers                    |                                                                             |
| Enrollment                      | Study flow diagram        | Description of study components and time frames                              |
|                                | Pictorial                 | Representation of study rationale                                           |
|                                | Welcome letter            |                                                                             |
| CHOICE Intervention             | Introduction              | Description of binder contents                                              |
| (participant binder)            | Folder index              |                                                                             |
|                                | Meal plan instructions    |                                                                             |
|                                | Sample meals              | Breakfast, lunch and dinner for low carbohydrate and low fat diets used for assessment of dietary preference |
|                                | 2-week initiation meal plans | 14 days of pre-compiled meals plus full shopping lists                         |
|                                | Interchangeable meal plans | 42 days' worth of interchangeable options for each meal; includes meals requiring recipes plus snack and dessert options |
|                                | Cookbook                  | Recipes and instructions                                                     |
|                                | Eating out options        | Local restaurants and common chain food establishments; 300, 400, 500 and 600 calorie choices |
|                                | Frozen meal options       | Frozen meals available commercially plus supplementary side dishes and snacks to achieve desired macronutrient content and calorie goals |
|                                | Snack Options             | 100 calorie snack options for addition to lower calorie meal options (e.g. additions to breakfast meal for use as a lunch meal) |
|                                | Post Blood Draw Snacks    | Snack options appropriate to meal plan and calorie goals following clinic venipuncture |
|                                | Quick Reference Guide     | Refrigerator magnet reference guide for available meals                     |
|                                | Blank shopping list& meal | Resources to support meal planning and time management                        |
|                                | planning template         |                                                                             |
|                                | Exchange list             | List of appropriate exchanges for commonly used foods from each food and discretionary food group (meat/ protein, dairy, vegetables, fruits, grains/ cereals, fats, sugars, processed snack items) |
|                                | Alcohol-step equivalents  | Step equivalents for commonly consumed alcoholic drinks; Daily step goals increased for consumption of any alcoholic beverage |
| Self Monitoring                | One week physical activity | Completed prior to allocation to intervention or control in order to determine likelihood of compliance |
|                                | and meal record           |                                                                             |
|                                | Meal and activity log     | Intervention food record (record meal code plus any deviations from the meal plan); steps/day |
|                                | ActiHeart/ Pedometer      | Participant instructions for physical activity monitoring                   |
|                                | instructions              |                                                                             |
|                                | America On The Move       | Guide to step equivalents for use in reporting steps/day                     |
|                                | resources                 |                                                                             |
|                                | Goal record sheet         | Participant diet and physical activity weekly goal record                    |
| Educational/ Support Materials  | ‘Preparing to start your CHOICE diet’ | Instructions for preparing to engage in a weight loss program including time and meal management, cooking and food storage preparation, and building social support |
|                                | Keeping track handout     | Instructions for food, physical activity and weight monitoring, and goal setting |
|                                | Weight management handbook | Weight management support resources handbook based on a systematic review of the weight loss literature |
|                                | SPRI Xertube and exercise | Guidance on safe home-based resistance training and building exercise capacity |
|                                | instructions              |                                                                             |
|                                | BMI chart                 | For use in weight monitoring                                                |
|                                | Participant contract      | Weight loss contract signed by participant and Registered Dietitian          |
|                                | Travel nutrition meal plan | Airport meal options, easy travel meals, and travel nutrition tips            |

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Benefit increases or plateaus with increasing weight loss or the achievement of BMI < 25kg/m². While metabolic abnormalities associated with cardiovascular disease and type-2 diabetes,
common co-morbidities of breast cancer survivors, are improved with weight loss within the 
range of 5 to 10% of initial body weight, overall mortality rates and cancer and cardiovascular 
disease specific death rates are lower in the general population when body mass index is in the 
normal range (18.5 to 24.9 kg/m²)[30,32–34]. To our knowledge there are no data to indicate 
that this relationship does not apply to breast cancer survivors; therefore, we encouraged 
CHOICE participants to achieve a body mass index of 22 to 23 kg/m² as a target for maximizing survival benefit.

In evaluating the anthropometric data, we recognized that no metrics are generally used to 
compare the success of weight loss programs, which is particularly important in the private 
practice setting since the staff resources committed to support weight loss can be considerable. 
Typical weight loss results (Table 2; Fig 2) fail to provide information about how long it takes 
for participants to reach weight loss benchmarks, making it difficult to compare various weight 
loss programs. We tackled this issue recognizing that achieving a loss of initial body weight of 5 
or 10% are recognized benchmarks of clinically meaningful weight loss [30]. Time to event 
analysis was utilized to compare the effects of dietary pattern on achieving these benchmarks. 
Median time to loss of ≥ 5% of baseline body weight was 2 months (95% CI = 1 to 3 months, 
Fig 4). Moreover, median time to loss of ≥ 10% of baseline body weight was 4 months (95% 
CI = 3 to 5 months). Ten percent weight loss is a level of success infrequently observed in 
weight loss interventions and to our knowledge the speed at which half of the study population 
reached this standard of success has not been reported in a postmenopausal cohort of cancer 
survivors [12,13]. Speed or intensity of weight loss is significantly impacts the level of resources 
that are needed for a successful program.

In evaluating the literature, we also recognized that the magnitude of variation among par-
ticipants in a weight loss program is difficult to visualize. We found no examples of the charac-
terization of variability among individuals within a cohort during progressive months of a 
weight loss program. For this purpose, we used box plots into which dot density data were inte-
grated as a graphic visualization tool. The box plot analyses (Fig 3) show that the consistency 
and magnitude of weight loss declined as the time on study progressed. These data are consis-
tent with the concept that interval-based weight loss might be a more expedient weight loss ap-
proach, a concept being evaluated in an ongoing clinical trial in Europe [35].

**Strengths and limitations**

This trial had a number of strengths including monthly assessment of body weight and compo-
sition during which weight loss counseling occurred, and the use of a structured plan of inter-
changeable menus and recipes. The use of the print-based meal plan may have been so effective 
because it was paired with both physical activity and behavior modification (step goals and 
self-monitoring of weight and diet) and frequent contact with study staff monthly (Summa-
rized in Table 5). Limitations include the fact that the study was neither double blinded nor 
randomized; thus, the possibility that association between diet intervention and weight loss 
may have been impacted by unknown or unmeasured confounding factors cannot be ruled 
out. While the results may not be generalizable to the population as a whole, it can be argued 
that our findings are more generalizable than standard RCTs in the breast cancer survivor pop-
ulation which is the focus of our work [24,36]. Thus, designing weight loss program based on 
cancer survivor preferences appears to lead to greater weight loss compared to standard pro-
grams [13] and is feasible in this population.
Conclusions
Clinically meaningful weight loss was achieved in greater than 92% of a population of breast cancer survivors using a program developed and implemented in a private practice setting. Loss of body weight and fat mass was rapid and substantial irrespective of dietary approach when a structured program was provided with monthly anthropometric assessment and weight loss counseling. Given the utility of the CHOICE weight loss program and the limitations of the study design, assessment of the transportability of the intervention approach is required.

Supporting Information
S1 CONSORT Checklist. CONSORT Checklist. (PDF)
S1 Protocol. Trial Protocol. (PDF)

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Author Contributions
Conceived and designed the experiments: HJT SMS. Performed the experiments: HJT SMS MCP JNM DP. Analyzed the data: HJT PW SGL. Contributed reagents/materials/analysis tools: PW JNM. Wrote the paper: HJT SMS SGL.

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