Weight loss intervention trials in women with breast cancer: a systematic review

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Abbreviations:

RCT, randomized controlled trial; WINS, Women's Intervention Nutrition Study; WHEL, Women's Healthy Eating and Living study; QOL, quality of life; PA, physical activity; LBM, lean body mass; DXA, dual-energy x-ray absorptiometry; NR, not reported; IGF, insulin-like growth factor; CRP, C-Reactive Protein; TNF, tumor necrosis factor; IL, interleukin; VEGF, vascular endothelial growth factor; SHBG, sex hormone binding globulin; BMD, bone mineral density

ABSTRACT

Obesity has been associated with poor health outcomes in breast cancer survivors. Thus, weight loss is recommended for overweight and obese survivors. We systematically reviewed studies (published up to July 2013) that evaluated behaviorally-based, weight loss interventions in women with breast cancer exclusively. Completed randomized trials, single-arm trials and ongoing trials were reviewed. Within-group and between-group differences for weight loss were extracted, as was data on secondary outcomes, i.e., clinical biomarkers, patient-reported outcomes, adverse events. Ten completed randomized trials, four single-arm trials and five ongoing trials were identified. Statistically significant within-group weight loss was observed over periods of 2-to-18 months in 13 of the 14 trials, with six randomized and two single-arm trials observing mean weight loss ≥5%. Clinical biomarkers, psychosocial and patient-reported outcomes were measured in a small number of studies. No serious adverse events were reported. Only two trials assessed maintenance of intervention effects after the end-of-intervention and none reported on cost-effectiveness. The studies included in this review suggest that weight loss is feasible to achieve and safe in women following treatment for breast cancer. Future studies should assess (and be powered for) a range of biomarker and patient-reported outcomes, and be designed to inform translation into practice.

INTRODUCTION

Over 50% of breast cancer survivors in Western countries are overweight or obese (1-4). Furthermore, most women undergoing breast cancer treatment will gain weight either during or following treatment (5). Excess body weight at diagnosis is associated with poorer breast cancer outcomes, with meta-analyses of observational studies reporting 20-43% higher risk of breast cancer-specific and overall mortality in obese women compared to healthy weight women; data are similar for pre- and post-menopausal women (6; 7). Obese women also have a 46% higher risk of distant metastases (8) and more than double the risk of any recurrence (9). The effect of post-diagnosis weight gain has been mixed (5; 10; 11).

The association between obesity and survival is variable across sub-groups, with no significant associations observed in women with triple negative breast cancer for either recurrence or overall survival (12; 13). Studies in specific ethnic groups, such as African-Americans and Hispanics, have shown weaker associations than those observed among Caucasians (14-16).

However, it is still unknown whether intentional weight loss improves outcomes for women with breast cancer. The Women's Intervention Nutrition Study (WINS; n=2,437) evaluated, in a randomized controlled trial (RCT), the impact on disease-free survival of a low-fat dietary intervention (individual face-to-face counseling sessions, of decreasing frequency over five years) compared to control (17). Although weight loss was not targeted, women in the intervention lost ~4% of initial body weight, and experienced lower rates of recurrence (HR = 0.76; 95% CI 0.60, 0.98), with a suggestion that this effect was stronger in women with estrogen receptor-negative (HR = 0.58; 95% CI 0.37, 0.91) and progesterone receptor-negative (HR = 0.54; 95% CI 0.35, 0.83) disease (17). In contrast, the Women's Healthy

Eating and Living (WHEL) study (n=3,088), did not observe differences in recurrence (HR = 0.96; 95% CI 0.80, 1.14) or survival (HR = 0.91, 95% CI 0.72, 1.15) with a low-fat, high fruit and vegetable diet (individual telephone counseling sessions, of decreasing frequency over four years), however participants were on average weight stable (18). Although other differences exist between the trials (19), weight loss in the WINS trial is a possible mechanism behind the lower recurrence.

Leading cancer organizations recommend that cancer survivors achieve and maintain a healthy body weight and promote modest weight loss (5-10% body weight) for those who are overweight/obese (20; 21). These recommendations are primarily driven by cancer survivors' substantial comorbidity (e.g., cardiovascular disease and diabetes), and the favorable influence of weight loss on these (22). Nevertheless, very few women are advised to manage their weight and improve their lifestyles by their oncologists (23; 24). Evidence on the benefits and (lack of) harms of intentional weight loss for women following treatment for breast cancer (10) is needed to support implementation of such programs as part of routine follow-up care.

The number of trials of weight loss interventions in breast cancer, while increasing, is still small, especially when compared to those on exercise and breast cancer, which have demonstrated benefits both during and after treatment on fatigue, depression, quality of life (QOL) and physical functioning (25; 26). Further, there is currently no systematic review on the benefits of weight loss across various breast cancer outcomes. Our aim was to systematically review the evidence from weight loss intervention trials in women with breast cancer. The review sought to identify the magnitude of weight loss achieved and the effect on breast cancer-related and general health outcomes, including anthropometric measures,

treatment-related side-effects, psychosocial indices, clinical biomarkers, changes to dietary intake and physical activity (PA), and adverse events.

METHODS

Search strategy and eligibility criteria

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (27), articles were identified through a structured search of PubMed, EMBASE and Web of Science up to July 1, 2013 with no date restrictions, limited to English-language. The following search terms were used to search titles and abstracts: [‘intervention’ OR ‘program*’ OR ‘trial’] AND [‘RCT’ OR ‘random*’ OR ‘control*’ OR ‘condition’] AND [‘breast’ AND (‘cancer’ OR ‘neoplasm’ OR ‘carcinoma’ OR ‘malignan*’)] AND [‘weight loss’ OR ‘weight-loss’ OR ‘weight management’ OR ‘weight control’ OR ‘weight maintenance’ OR ‘weight maintaining’ OR ‘weight change*’ OR ‘weight reduc*’].

Key author searches and manual searches of reference lists of included studies and recent review articles were conducted. Titles and abstracts were screened by one author (MMR) to determine eligibility. If unclear, the full-text was independently reviewed by two authors (MMR/COT), with differences resolved by discussion. For inclusion, the study had to be conducted exclusively in women with breast cancer, and report on the outcomes of an intervention trial evaluating a weight loss (not weight gain prevention) intervention. The intervention had to be behaviorally-based, i.e., promotion of an energy-restricted diet with or without PA, not weight loss as a result of pharmacologic or surgical intervention. RCTs were of primary interest, and could have included an intervention and control group or two intervention groups. Single-arm (pre- post-test) intervention studies also were included.

Ongoing trials identified in the search (e.g., protocol publications) were also reviewed, as these included a number of large-scale trials with survival endpoints.

Data extraction

Data were extracted and tabulated by one author (COT) and independently reviewed by another (MMR), with differences resolved by discussion. Extracted data included: study design; country; sample size; eligibility criteria (age; menopausal status; BMI; stage; time since diagnosis/treatment); participant characteristics (mean age, BMI, time since diagnosis, ethnicity); retention rate; description of the study groups (intervention: duration, frequency and number of contacts, modality of delivery, behavioral targets; details of treatment provided to control/usual care groups); and outcomes measured. Within- and between-group changes in weight with significance were extracted (reported as kilograms or percent of initial body weight). If within-group significance was not reported this was calculated from mean and standard deviation of change, if available. If change in body weight was not expressed as percent of initial body weight, estimates from the absolute weight change in kilograms and baseline weight were calculated. Studies were classified by mean within-group weight loss of ≥5% of initial body weight (20). Within-group and between-group significance for changes in other outcomes of interest also were extracted. Within-group changes in clinical biomarkers were expressed as percent change from baseline ([change/baseline value]*100), and their associations with magnitude of weight loss were considered. The primary focus was on end-of-intervention outcomes. If information was missing or unclear, authors and clinical trials registers were consulted.

Risk of bias of included studies was independently assessed by two authors (MMR/COT) using a 10-item checklist (28; 29) (Table S1), based on the Consolidated Standards of

Reporting Trials (CONSORT) statement (30), and the Cochrane Handbook for systematic reviews of interventions (31). Each item was scored 'present' [1-point], 'absent' [zero-points] or 'unclear or inadequately described' [zero-points], with disagreements resolved by discussion. Each study was assigned a risk of bias category: high risk [0-3], moderate risk [4-7] and low risk [8-10]. Risk of bias was assessed for single-arm trials against six criteria (Table S2), and was categorized based on: high risk [0-2], moderate risk [3-4] and low risk [5-6]. Due to the small number of studies, trials were not excluded based on the risk of bias assessment.

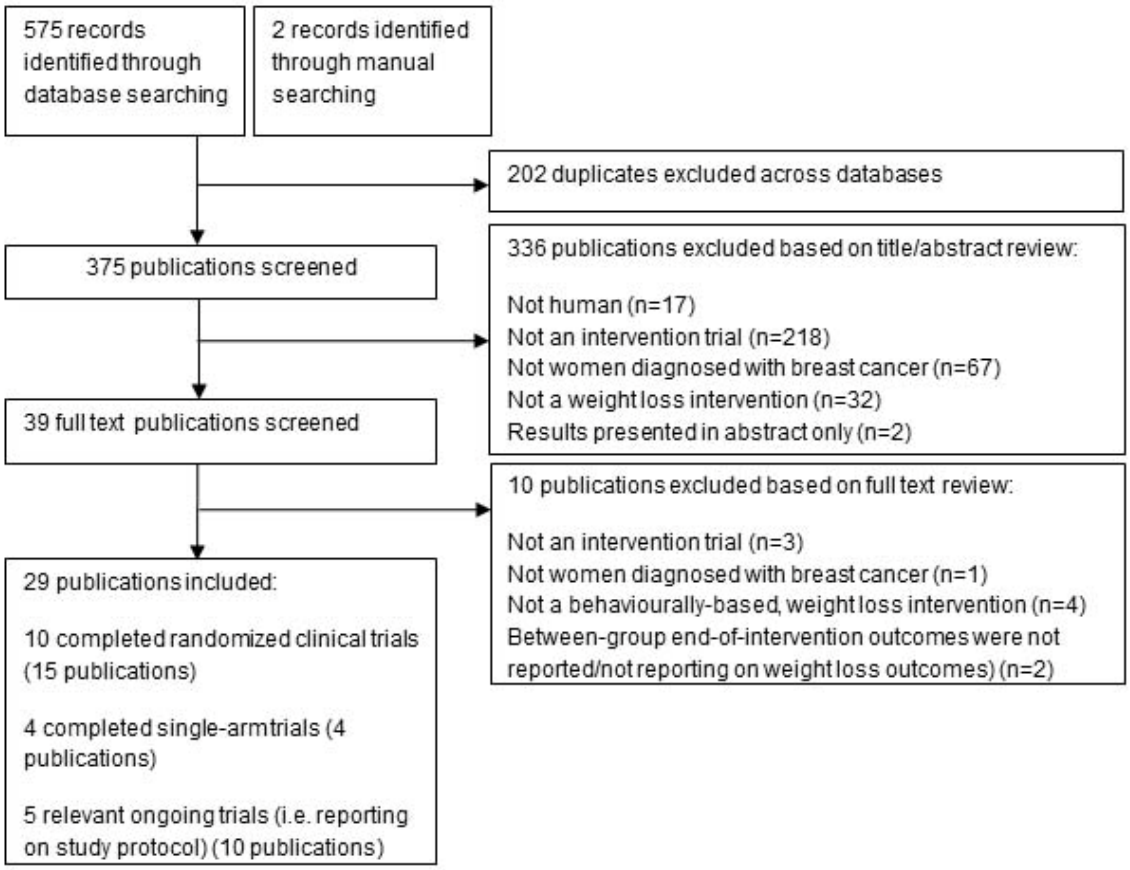
RESULTS

A total of 577 articles were identified (Figure 1). After removing duplicates (n=202), and excluding articles based on title and abstract (n=336), 39 publications were closely examined. Ten were subsequently excluded, leaving 29 publications included in the review – 10 completed RCTs (15 publications), four single-arm intervention trials and five ongoing trials (10 publications).

Completed randomized clinical trials

Details of the 10 RCTs included in the review are shown in Table 1. The methodological quality of these was quite poor. Risk of bias was considered high in five (32-36), moderate in four (37-40), and low in only one (41) (Table S1).

Figure 1. PRISMA flow chart of studies through the review process



Sample sizes ranged from 24 (35; 37) to 102 (32), with half recruiting <50 participants (33; 35-38). Six-of-10 trials recruited both pre- and post-menopausal women (33; 34; 37-39; 41), two recruited only post-menopausal women (32; 36) and two were unspecified (35; 40). Only four studies reported mean time post-diagnosis for participants,(34; 36-38) ranging from 3.5-5.6 years. Only one trial limited recruitment to a particular subtype of breast cancer and here, the defined subtype was broadly classified as estrogen receptor-positive (36). Seven-of-ten trials reported on ethnicity; five of these recruited Caucasians predominantly (33; 34; 36; 39; 41), and two exclusively recruited African-Americans or Hispanics (37; 38).

Six-of-10 trials evaluated weight loss interventions addressing both diet and PA (33; 34; 37-39; 41) with the other four addressing diet only (32; 35; 36; 40). While most interventions

were delivered face-to-face, three studies evaluated interventions delivered via telephone (33; 37; 39). Seven-of-10 trials evaluated a weight loss intervention compared to a control group (32-35; 38; 40; 41), with two of these studies also comparing to at least one other intervention group (33; 40). Three studies compared two intervention groups only (36; 37; 39). Intervention duration was less than 6-months in two trials (34; 35), 6-months in four trials (36; 38; 40; 41) and 12-months or longer in the other four (32; 33; 37; 39). Only one trial evaluated outcomes after a period of no intervention contact (38).

Single-arm trials

Details of the four single-arm trials included in the review are also shown in Table 1. One trial was considered to have high risk of bias (42) with the remaining three having moderate risk (43-45) (Table S2). The four single-arm trials recruited between 10-34 participants. Three included both pre- and post-menopausal women (42; 44; 45) and one included post-menopausal women only (43). Participants were recruited, on average, 2-3 years after treatment completion (43; 44). One study recruited African-American women exclusively (45), with the others recruiting predominantly Caucasians (43; 44) or not reporting on ethnicity (42). Three-of-four trials evaluated a 6-month, group-based intervention (43-45); in one, the group sessions were conducted via conference call (43). One study evaluated an 8-week diet and exercise intervention with thrice weekly supervised exercise sessions (42). Only one study followed-up participants post-intervention to assess whether changes in outcomes were maintained (44).

Weight and anthropometric outcomes

Weight change outcomes are shown in Table 1. Significant within-group weight loss was observed in intervention groups in all RCTs and single-arm trials except for one, where

within-group significance could not be calculated (37). Mean weight loss of ≥5% initial body weight was observed in at least one of the intervention groups in six-of-10 RCTs (32-34; 36; 39; 40) and two of the single-arm trials (43; 44). Of the seven RCTs that compared the weight loss intervention to a control group, all except one (41) observed a statistically significant effect for weight loss (32-35; 38; 40). Of the studies that compared different weight loss interventions (33; 36; 37; 39; 40), no significant differences in weight loss were observed, with the exception of the study by Harris et al (39).

Five-of-10 RCTs and three-of-four single-arm trials also reported on changes in waist circumference (34; 36; 38; 39; 41-44); six RCTs and two single-arm trials reported changes in adiposity (33; 34; 36; 38; 40-42; 44); and three RCTs and one single-arm trial reported changes in lean body mass (LBM) measured via Dual-energy X-ray Absorptiometry (DXA) (34; 36; 38). Waist circumference was significantly reduced in all of the intervention groups and percent body fat significantly reduced in all except one (41). No significant changes in LBM were observed in two trials (34; 38), whereas significant reductions in LBM were observed in the other two trials (36; 44).

Clinical biomarkers

Six-of-10 RCTs and three-of-four single-arm trials measured clinical biomarkers (34; 36; 38; 39; 41; 46). Glucose and/or lipids were measured in all except two trials (42; 43); changes in these were inconsistently associated with weight loss both across the range of biomarkers assessed within studies and across studies. The most consistent changes were reductions in LDL-cholesterol and glucose. Two RCTs measured blood pressure (36; 41) – in one trial systolic blood pressure reduced in the low fat diet intervention but not the reduced carbohydrate diet group, with no change in diastolic blood pressure in either (36); whereas in

the other trial diastolic but not systolic blood pressure was significantly lower in the intervention group compared with control (41).

Five RCTs (36; 38; 41; 46; 47) and three single-arm trials also measured biomarkers that have been associated with breast cancer progression (i.e., insulin pathways, adipokines and inflammatory markers) (48). Changes in these are shown in Table 2. Six trials measured insulin and/or insulin resistance (36; 38; 41; 43; 44; 46). Trials reporting weight losses of ≥5% observed reductions in insulin and insulin resistance of 15-40% (36; 43; 44; 46). Insulin-like growth factor-1 (IGF-1) and IGF binding proteins were measured in two trials (38; 41), which reported weight losses of <5% and no within- or between-group differences were observed (38; 41). Changes in leptin were assessed in three trials (41; 43; 46); with leptin concentrations on average reduced by 12-40% in intervention groups. Total adiponectin was measured in two trials (38; 43). There was no significant within- or between-group difference in adiponectin, and adiponectin concentrations did not change in the expected direction with magnitude of weight loss in these trials.

Table 1. Trials of weight loss interventions in women with breast cancer*

Study/ Bias Score[‖]	Sample	Study Arms/Intervention Characteristics	Outcomes/Comments
Randomized controlled trials			
De Waard 1993 (32) The Netherlands & Poland Risk of bias: 3/10 (high)	102 post-menopausal women Stage NR (no signs of distant metastases) Mean time post-diagnosis NR (recruited soon after recovery from surgery/radiotherapy) Mean BMI NR (eligibility: BMI ≥27kg/m^2) Mean age NR (eligibility: 50-69yrs) Ethnicity NR Recruited through hospitals	a) Initial individual, face-to-face dietitian-delivered counselling with variable follow-up for 1 or 3yrs; aim of 10kg weight loss; balanced diet of 1500kcal/d; (1000kcal/d if insufficient weight loss was noted) b) Control (no details reported) Intervention duration/follow-up: 1-3yrs	a) approx. -6kg. b) NR Retention: 73.5% Missing data: completers analysis
Djuric 2002 (33) USA Risk of bias: 3/10 (high)	48 pre & post-menopausal women Stage I or II breast cancer Mean 4yrs post-diagnosis (free of recurrence) Mean BMI 35.5kg/m² (eligibility: 30-44kg/m²) Mean age 52yrs (eligibility: 18-70yrs) 73.0% Caucasian; 25% African American	a) Weight Watchers: weekly group meetings for 1yr (coupons provided free of charge) b) Individualized: telephone dietitian-delivered contact weekly (months 1-3), biweekly (months 4-6), and monthly (months 7-12). Monthly group, face-to-face meetings were encouraged, not required. Written materials/brochures provided monthly. Specified energy intake (calculated from current body weight and deficit of 500-1000kcal/d); 20-25% energy from fat; 20% protein; 5 servings/d of fruit & vegetables; 30-45min/d moderate physical activity most days of week; pedometers provided for self-monitoring and goal-setting c) Comprehensive: both a) and b) for 1yr	Change from baseline to 12-months: a) -2.7 ± 2.1 kg b) -8.0 ± 1.9 kg[†] c) -9.5 ± 2.7 kg[†] d) +1.1 ± 1.7 kg b vs. d[‡]; c vs. d[‡] %BF[c] a vs. c[‡], b vs. d[‡] and c vs. d[‡] Retention: 81.3% Missing data: unclear

	Recruited through direct mail; press releases; brochures at breast clinics	d) Control: National Cancer Institute's 'healthy eating' pamphlets Intervention duration: 12mo Post-intervention follow-up: no	
Mefferd 2007 (34) USA Risk of bias: 2/10 (high)	85[§] pre & post-menopausal women Stage I-IIIa breast cancer Mean 3.5yrs post-diagnosis (diagnosed within 14yrs) Mean BMI 31.0kg/m² (eligibility: ≥25kg/m^2) Mean age 56yrs (eligibility: ≥18yrs) 93% Caucasian Recruited through cancer registry, clinician referral, community advertising (local newspaper, community events)	a) Group, face-to-face weekly sessions for 16wks and bi-weekly telephone counselling for weeks 1-2 then weekly. Goal of 500-1000kcal/d energy deficit by reducing energy density; high-fibre vegetables, whole grains and fruit encouraged; goal of 60min/d of moderate to vigorous physical activity; strength exercise 2-3 times/wk; increased lifestyle activity (pedometer provided); cognitive behavioral therapy, goal setting, self-monitoring and cognitive restructuring; facilitator unclear b) Wait-list control: usual care Intervention duration/follow-up: 16wks[‖] Post-intervention follow-up: no	Change from baseline to 16 weeks: a) -5.7 ± 3.5 kg[†] b) -0.2 ± 4.1 kg a vs. b[‡] WC[a‡]; HC[a‡]; WHR; total BF (DXA)[‡]; trunk FM[‡]; leg FM[‡]; LBM Retention: 89.4% Missing data: completers analysis
Shaw 2007 (35) UK Risk of bias: 3/10 (high)	24[§] women with documented lymphedema secondary to breast cancer (menopausal status NR) No stage restrictions Mean time post-diagnosis NR (remission from cancer and no chemotherapy/radiotherapy in the previous 12mo) Mean BMI 32.0kg/m² (eligibility: ≥25kg/m^2)	a) Weight-reduction: individualized, dietitian-delivered dietary advice (frequency of contact unclear); energy deficit of 1000kcal/d; specific reduction of fat and refined carbohydrates; b) Control: healthy eating booklet Intervention duration/follow-up: 12wks Post-intervention follow-up: no	Change from baseline to 12 weeks: a) -3.3 ± 2.6 kg[†] b) 0.0 ± 3.0 kg a vs. b[‡] Skinfold thickness Retention: 87.5%

	Mean age 60yrs (eligibility: NR) Ethnicity NR Recruited from a lymphedema Clinic and the Lymphedema Support Network		Missing data: completers analysis
Shaw 2007 (40) UK Risk of bias: 4/10 (moderate)	64[§] women with documented lymphedema secondary to breast cancer (menopausal status NR) No stage restrictions Mean time post-diagnosis NR (remission from cancer and no chemotherapy/radiotherapy in the previous 12mo) Mean BMI 27.2kg/m² (eligibility: NR) Mean age 65yrs (eligibility: NR) Ethnicity NR Recruited through a lymphedema clinic	a) Weight-reduction: individualized, dietitian-delivered advice (frequency of contact unclear); reduced-energy intake of 1000-1200kcal/d; specific reduction of high fat and refined carbohydrate foods; b) Low-fat diet: individualized, dietitian delivered advice (frequency of contact unclear); 20% energy from fat; recommended increased carbohydrate intake to maintain energy intake; c) Control: continue with habitual diet Intervention duration: 6mo Post-intervention follow-up: no	Change from baseline to 6 months: a) -4.0 ± 2.7 kg[†] b) -2.6 ± 3.0 kg[†] c) -0.6 ± 3.0 kg a vs. c[‡]; b vs. c[‡] Skinfold thickness (sum of 4 sites)[‡], %BF[‡] Retention: 79.7% Missing data: completers analysis
Djuric 2009 (37) USA Risk of bias: 4/10 (moderate)	24 pre & post-menopausal women Stage I-IIIa breast cancer Mean 5.6yrs post-diagnosis (diagnosed within 10yrs; no recurrence/second primary tumour) Mean BMI 36.6kg/m² (eligibility: 30-45kg/m^2)	All participants (initial 6-months): one face-to-face dietitian-delivered counselling session, then telephone sessions – weekly (months 1-3) then biweekly (months 4-6). Weight watchers coupons provided for weekly attendance and a monthly newsletter. Aim for 10% body weight loss; energy deficit of 500-1000kcal/d; 20-25% energy from fat; 20% protein; 6-8 serves/d of fruit and vegetables; 30min of exercise on at least 5 days.	Change from baseline to 18 months: a) -1.9% (sd NR) b) -1.5% (sd NR) a vs. b (ns) Retention: 71.0%

	Mean age 55yrs (eligibility:18-70yrs) 100% African American Recruited through clinics; presentations; mailing to breast cancer support group; newspaper adverts	a) Dietitian counselling only: continued intervention with monthly telephone calls for 12 months b) Spiritually-tailored dietitian counselling: in addition, telephone-delivered spiritual counselling – weekly (months 1-3), biweekly (months 4-6) then monthly (months 7-12) Intervention duration/follow-up: 18mo Post-intervention follow-up: no	Missing data: completers analysis
Thomson 2010 (36) USA Risk of bias: 3/10 (high)	40 post-menopausal women Stage I or II ER+ breast cancer Mean 3.7yrs post-diagnosis (treatment completed within previous 4yrs) Mean BMI 31.8kg/m² (eligibility: 25.0-34.9kg/m²) Mean age 56yrs (eligibility: 50-60yrs) 82% Caucasian Recruited through a cancer center	a) Low fat/High carbohydrate diet: individualized, face-to-face, dietitian-delivered counselling; weekly for 6 weeks followed by the 6 month intervention. Individualized energy intake (deficit of 500kcal/d); 55-60% energy from carbohydrates; 25% fat; 15-20% protein b) Reduced carbohydrate diet: individualized, face-to-face, dietitian-delivered counselling; weekly for the first 6 weeks of the 6 month intervention. Individualized energy intake (deficit of 500kcal/d); 35% energy from carbohydrates; 25-30% protein; 35-40% fat; instructed to reduce carbohydrates to <30g/d in first 2wks to induce ketosis Intervention duration/follow-up: 6mo Post-intervention follow-up: no	Change from baseline to 6 months: a) -6.3 ± 5.6 kg† b) -5.9 ± 4.1 kg† a vs. b (ns) WC[a,b], WHR, %BF (DXA)[a,b], appendicular LBM (DXA)[a,b] Retention: 80.0% Missing data: baseline observation carried forward
Greenlee 2012 (38) USA Risk of bias: 5/10 (moderate)	42 pre & post-menopausal women Stage 0-IIIa breast cancer Mean 4.1 years post-diagnosis (treatment completed at least 6mo prior; no recurrence/metastasis)	a) Curves weight management program- (commercial gym/weight loss program); free gym membership; 3 face-to-face exercise training sessions with a Curves trainer and : 6 x 1hr weekly, group sessions with Curves instructor for nutrition course (commenced about 1 month after exercise program); target goal of 3-5 days/wk exercise session at gym; 1200kcal/d for 1-	Change from baseline to 6 months: a) -2.9 ± 3.2 kg† b) -1.4 ± 2.5 kg† a vs b‡

	mean BMI 33.2kg/m² (eligibility: >25 kg/m²) Mean age 51yrs (eligibility: 21-70yrs) 79% Hispanic; 21% African American Recruited through a breast oncology clinic	2 wks then 1600kcal/d; 45% energy from protein; 30% carbohydrates; 25% fat; weekly motivational telephone calls from instructor during 6 week nutrition course. b) Wait-list control arm Intervention duration/follow-up: 6mo Post-intervention follow-up: yes – 6mo (immediate intervention arm only)	WC[a], HC, % BF (DXA) [a], FM kg (DXA) [a], LBM kg (DXA) Retention: 90.5% Missing data: completers analysis
Harris 2012 (39) USA Risk of bias: 4/10 (moderate)	52[§] pre & post-menopausal women Stage I-IIIa breast cancer Mean time post-diagnosis NR (treatment completed within previous 2-36mo) Mean BMI 31.9kg/m² (eligibility: 25-45kg/m²) Mean age 53yrs (eligibility: 30-75yrs) 80% Caucasian Recruited through advertisements; physician referrals; breast cancer survivor groups	a) [¥]Group-based: 16 x 60-90min, group, face-to-face sessions over 6-months; facilitated by a trained interventionist; goal of 150 min/wk moderate physical activity; dietary goals to achieve 0.5-1kg weight loss/wk (following Diabetes Prevention Program guidelines). Months 7-12 – monthly, individual telephone contacts with interventionist. b) [¥]Telephone-based: individual, 15-60min, weekly telephone contacts for 6-months; delivered by commercial behavior change company personnel; physical activity and dietary goals same as group (a). Months 7-12 – monthly telephone Intervention duration/follow-up: 12mo Post-intervention follow-up: no	Change from baseline to 12 months: a) -2.0 (sd NR) kg b) -5.0 (sd NR) kg[†] a vs. b (NR) WC (NR) Retention: 78.8% Missing data: completers analysis
Scott 2013 (41) UK	90 pre & post-menopausal women Stage I-III breast cancer Mean time post-diagnosis NR (treatment completes within previous 3-18mo)	a) 24 weeks, 3 x weekly supervised exercise sessions (30 mins aerobic + 10-15 mins resistance exercise); one-to-one individualized dietary advice session + written information; + weekly, small group, nutrition education sessions; goal of 0.5kg weight loss/wk;	Change from baseline to 24 weeks (median [IQR]) a) -1.1 [-2.9, -0.2] kg[†] b) -0.4 [-1.8, 0.7] kg a vs. b (ns)

Risk of bias: 8/10 (low)	Mean BMI 30.3kg/m^2 (eligibility: >25kg/m^2) Mean age 56yrs (eligibility NR) 98% Caucasian Recruited through hospital clinical trials center, local cancer support services, media or word of mouth	energy intake (deficit of 600kcal/d); 25% energy from fat; at least 5 serves/d of fruit and vegetables. b) Control: general healthy eating booklet Intervention duration/follow-up: 24wks Post-intervention follow-up: no	WC[a], WHR[a], %BF (BIA) Retention: 87.8% Missing data: multiple imputation
Single-arm trials			
McTiernan 1998 (42) USA Risk of bias: 2/6 (high)	10 pre & post-menopausal women Stage I-II breast cancer Mean time post-diagnosis NR (range 1-5yrs post-diagnosis; treatment completed within previous 4mo) Mean BMI NR (eligibility: >25 kg/m²) Mean age NR (range: 40-74yrs; eligibility: 25-75yrs) 90% Caucasian Recruited through oncology practices	3 x weekly, individual or group, face-to-face supervised exercise sessions for 8wks delivered by an exercise physiologist; individually prescribed exercise program; between wks 4-8 patients exercise at home on non-monitored days; gradual increase to 30-45 mins/d moderate-intensity aerobic activity/ day, 6 days/wk. 1 x individual or group, face-to-face counselling session delivered by nutritionist; low-fat diet (20% energy from fat); high fruit and vegetable intake (8+/day) 1 x telephone call in week 3 delivered by a nutritionist to assess adherence and provide additional counselling Intervention duration: 8 weeks Post-intervention follow-up: no	Weight: -1.2 ± 1.4 kg[†] WC[†]; HC[†]; %BF (BIA)[†]; % LBM (BIA)[†]; Retention rate= 90% Missing data: completers analysis
Stolley 2009 (45) USA Risk of bias: 4/6 (moderate)	23 pre & post-menopausal women Stage I-III breast cancer Mean time post-diagnosis NR (treatment completed at least 6 months prior) Mean BMI 34.1kg/m² (eligibility: ≥25kg/m²)	2 x weekly, group, face-to-face classes for 6 months; 1 x 2hr class (address knowledge, attitudes, barriers, facilitators etc; + 60min exercise class) and 1 x 1hr exercise class delivered by local instructor Intervention duration: 6mo Post-intervention follow-up: no	Weight: -2.5 (-3.9, -1.1) kg[†] Retention rate= 87.0% Missing data: completers analysis

	Mean age 51yrs (eligibility: ≥18yrs) 100% African American Recruited through local chapters of national breast cancer support organisations		
Befort 2012 (43) USA Risk of bias: 4/6 (moderate)	34 rural, post-menopausal women Stage I-IIIc breast cancer Mean time post-diagnosis NR (Mean 3.1yrs since treatment completion; treatment completed within previous 10yrs) Mean BMI 33.7kg/m² (eligibility: 27-45kg/m²) Mean age 59yrs (eligibility: <75yrs) 97% Caucasian Recruited through rural cancer centers	24 x 1hr weekly, group, telephone contacts using conference call, delivered by dietitian or clinical psychologist. Goal of 10% weight loss; 1000kcal reduction/d; ≥5 serves fruit & vegetables/d, approved pre-packaged frozen dinners (2/d) or equivalent (soup, portion-control meal), shakes (2/d, provided); gradual increase to 225min moderate physical activity/wk Intervention duration: 24wks Post-intervention follow-up: no	Weight: -11.6 ± 6.5 kg† WC† Retention rate= 91% Missing data: completers analysis and baseline observation carried forward

Campbell 2012 (44) Canada Risk of bias: 4/6 (moderate)	14 pre & postmenopausal women Stage I-IIIa breast cancer Mean time post-diagnosis NR (Mean 2.1yrs since treatment completion; diagnosed within 5yrs; treatment completed within previous 3mo) Mean BMI 30.1kg/m² (eligibility: 25-35kg/m²) Mean age 55yrs (eligibility: >18yrs) Recruited through referral from their oncologist; word of mouth; poster advertising	16 x 2hr group, face-to-face, dietitian-delivered sessions; weekly (weeks 1-8) and bi-weekly (weeks 9-24); individual energy strategies provided based on weight loss goal of 7% baseline weight (specific amounts of energy were not prescribed); 20% energy from fat; gradual increase to 150min/wk of moderate to intense physical activity including 2 x 45min sessions/wk of supervised exercise Intervention duration: 24wks Post-intervention follow-up: yes (12 weeks)	Weight: -3.8 ± 5.0 kg[†] WC[†]; HC[†]; total FM (DXA)[†]; %BF (DXA)[†]; LBM (DXA)[†] Retention rate= 100% Missing data: completers analysis for some outcomes with missing data (n=10-13)

C-Reactive Protein (CRP) was measured in four trials (36; 38; 41; 44), with none reporting significant within- or between-group differences. Only one trial measured other inflammatory markers (TNFα, IL-6, IL-8, VEGF) and observed no between-group differences, despite significant between-group differences in weight loss (47). Two trials (41; 42) measured several sex hormones and observed no significant within- or between-group changes, though weight loss was minimal.

Psychosocial outcomes and treatment-related side-effects

Psychosocial indices and treatment-related side-effects are shown in Table 3. QOL was assessed in two of the RCTs (41; 49) and two single-arm trials (44; 45), with mixed effects. Two studies reported significant intervention effects on QOL (41; 44) (despite one trial observing minimal weight loss), one reported significant associations with weight loss (49), and one reported no significant change in QOL (45). Depression was measured in one RCT, with no significant difference in change in depression scores between the intervention groups (37); and in one single-arm trial which observed a significant improvement (43).

Three RCTs (35; 40; 49) and one single arm trial (43) assessed treatment-related side-effects. Excess arm volume as a measure of lymphedema was measured in two studies (35; 40), with one observing a significant reduction in the intervention group compared to control (35), whereas the other observed similar reductions across both intervention groups and the control group (40); baseline levels of excess arm volume were considerably higher in the latter study. In both trials, weight loss was significantly correlated with changes in excess arm volume (35; 40). Darga et al. (49) reported a significant association between weight change and fatigue at 12-months, but did not report between-group differences. Befort et al. (43) observed no significant change in fatigue or cognitive function, but observed statistically

significant improvements in body image and joint pain, and a trend toward reduced hot flashes, in their single-arm trial.

Dietary intake and physical activity

Seven RCTs reported changes in dietary intake (33; 35-38; 40; 41) and four reported changes in PA or fitness levels (34; 37; 38; 41). Two RCTs reported measuring PA, but did not report results (33; 36). Two did not report on either behavior (32; 39). All single-arm trials reported on changes in dietary intake and physical activity. Significant between- and within-group changes in these outcomes are shown in Table 3. In the studies which reported changes in dietary intake and/or PA, weight loss was generally supported by reductions in total energy intake and fat intake, and increases in PA.

Table 2. Changes in cancer-related biomarkers in randomized clinical trials and single-arm studies of weight loss interventions in women with breast cancer

Biomarker	Study/Author	Study group	N	% body weight loss	% change in biomarker	Sample & assay details
Insulin / Insulin resistance	Djuric 2002 & Jen 2004 (33,46)	a) Weight-watchers arm	8	a) -2.8%	Insulin: ↑13.2% HOMA-IR: ↑5.0%	Fasting blood sample Batch assay NR Insulin: Not clear Glucose: Not clear
		b) Individualized arm	9	b) -8.8%	Insulin: ↓23.2% HOMA-IR: ↓30.0%	
		c) Comprehensive arm	10	c) -9.5%	Insulin: ↓26.1% HOMA-IR: ↓17.6%	
		d) Control	12	d) +1.2%	Insulin: ↑17.7% HOMA-IR: ↑17.1%	
	Thomson 2010 (36)	a) Low-fat diet	21	a) -7.6%	Insulin: ↓28.3% HOMA-IR: ↓30.0% † HbA1c: ↓3.3%	Fasting blood sample Batch assay NR Assay NR
		b) Reduced-carbohydrate diet	19	b) -6.9%	Insulin: ↓15.5% † HOMA-IR: ↓16.7% † HbA1c: ↓1.7% †	
	Greenlee 2010 (38)	a) Curves program	20	a) -3.3%	Insulin: ↑4.5% HOMA-IR: ↑5.0%	Fasting blood sample Batch assays conducted Insulin: RIA Glucose: automated chemistry analyzer
		b) Wait-list control	17	b) -1.8%	Insulin: ↓5.6% HOMA-IR: ↓4.9%	
	Scott 2013 (41)	a) Weight loss intervention	43	a) -1.3%	HOMA-IR: ↑5.3%	Fasting blood sample Batch assays conducted Insulin: ELISA
		b) Control	40	b) -0.5%	HOMA-IR: ↑13.1%	
	Befort 2012 (43)	Weight loss intervention	31	-13.9%	Insulin: ↓42.9% †	Fasting blood sample Batch assays conducted ELISA

	Campbell 2012 (44)	Weight loss intervention	13	-4.9%	Insulin: ↓28.3% HOMA-IR: ↓30.3%	Fasting blood sample Batch assays conducted Assay NR
IGF & IGFBP	Greenlee 2010 (38)	a) Curves program	17	a) -3.3%	IGF-I: ↑15.1% IGFBP-1: ↑24.5% IGFBP-3: ↑13.3%	Fasting blood sample Batch assays conducted ELISA
		b) Wait-list control	21	b) -1.8%	IGF-I: ↑11.4% IGFBP-1: ↑19.5% IGFBP-3: ↑2.4%	
	Scott 2013 (41)	a) Weight loss intervention	43	a) -1.3%	IGF-I: ↓2.8% IGFBP-1: ↑11.8% IGFBP-3: ↓6.8%	Fasting blood sample Batch assays conducted ELISA
		b) Control	40	b) -0.5%	IGF-I: ↓2.0% IGFBP-1: ↑5.2% IGFBP-3: ↓2.7%	
Leptin	Djuric 2002 & Jen 2004 (33,46)	a) Weight-watchers arm b) Individualized arm c) Comprehensive arm d) Control	8 9 10 12	a) -2.8% b) -8.8% c) -9.5% d) +1.2%	↑3.0% ↓30.4% ↓41.6% † ↑14.3%	Fasting blood sample Batch assay NR Assay not clear
	Scott 2013 (41)	a) Weight loss intervention	43	a) -1.3%	↓11.9% *	Fasting blood sample Batch assays conducted ELISA
		b) Control	40	b) -0.5%	↑16.7%	
	Befort 2012 (43)	Weight loss intervention	31	-13.9%	↓42.5% †	Fasting blood sample Batch assays conducted ELISA
Adiponectin (total)	Greenlee 2010 (38)	a) Curves program b) Wait-list control	22 20	a) -3.3% b) -1.8%	↑18.2% ↑31.9%	Fasting blood sample Batch assays conducted RIA
	Befort 2012 (43)	Weight loss intervention	31	-13.9%	↑2.1%	Fasting blood sample Batch assays conducted

						ELISA
CRP	Greenlee 2010 (38)	a) Curves program	22	a) -3.3%	↑41.6%	Fasting blood sample
		b) Wait-list control	20	b) -1.8%	↑2.6%	Batch assays conducted
						High sensitivity CRP – automated chemistry analyzer
	Thomson 2010 (36)	a) Low-fat diet	21	a) -7.6%	↓9.1%	Fasting blood sample
		b) Reduced-carbohydrate diet	19	b) -6.9%	↓6.8%	Batch assay NR
						High sensitivity CRP - automated turbidimetry analyzer
	Scott 2013 (41)	a) Weight loss intervention	43	a) -1.3%	↑7.3%	Fasting blood sample
						Batch assays conducted
		b) Control	40	b) -0.5%	↑1.4%	Assay NR
	Campbell 2012 (44)	Weight loss intervention	13	-4.9%	↓44.4%	Fasting blood sample
						Batch assays conducted
						Assay NR
Other inflammatory markers	Mefferd 2007 & Pakiz 2011 (34,47)	a) Weight loss intervention	44	a) -6.8%	TNF-α: ↓8.5% †	Fasting NR
					IL-6: ↓17.6%	Batch assays conducted
					IL-8: ↑6.3%	ELISA
					VEGF: ↑14.3%	
		b) Wait-list control	24	b) 0.2%	TNF-α: ↓14.8% *	
					IL-6: ↓17.6%	
					IL-8: ↓2.2%	
					VEGF: ↑10.3%	
Sex Hormones	Scott 2013 (41)	a) Weight loss intervention	43	a) -1.3%	Estradiol: ↓7.5%	Fasting blood sample
					Estrone: ↑5.5%	Batch assays conducted
					Testosterone: 0%	Estradiol & estrone by ELISA
					SHBG: ↑5.0%	Testosterone & SHBG NR
		b) Control	40	b) -0.5%	Estradiol: ↓20.0%	
					Estrone: ↓0.9%	

	McTiernan 1998 (42)	Intervention	8	-1.5%	Testosterone: ↑6.2% SHBG: ↓1.2% Total estradiol: ↓12.5% Free estradiol: ↓5.4% Total estrone: ↑7.1% Estrone sulphate: ↓18.8% Total testosterone: ↓4.1% Free testosterone: ↓7.7% Androstenedione: ↓7.1% SHBG: ↓8.3% DHEA: ↓7.1% DHEA-Sulphate: ↓10.7%	Fasting blood sample Batch assays conducted Estradiol, estrone, testosterone & androstenedione by RIA SHBG & DHEA not clear

Table 3. Changes in psychosocial indices, treatment-related side-effects, dietary intake and physical activity reported in randomized clinical trials and single-arm trials of weight loss interventions in women with breast cancer

Study	Psychosocial indices & treatment related side-effects	Dietary intake	Physical Activity
Randomized Controlled trials			
de Waard 1993 (32)	-	-	-
Djuric 2002, Jen 2004 & Darga 2007 (33,46,49)	Quality of Life (FACT-Anemia): NR Fatigue (FACIT-Fatigue): NR	3 day food records: Energy intake [abc] Total fat (%E) [ab]	Physical activity logs: NR

Mefferd 2007 & Pakiz 2011 (34,47)	-	-	7-day physical activity recall Moderate-vigorous PA*
Shaw 2007 (35)	Lymphoedema (arm circumference measurements): Excess arm volume (%)*	7-day diary: Energy intake* Total fat (g/d)* Protein (g/d) Carbohydrates (g/d)*	-
Shaw 2007 (40)	Lymphoedema (arm circumference measurements or Perometer): Excess arm volume	7-day diary: Energy intake* Total fat (g/d and %E)* Protein (g/d) * Carbohydrates (g/d)*	-
Djuric 2009 (37)	Depression (CES-D): Depression score	Food frequency questionnaire (Block): Total fat (%E) [ab] Fruit (serves/1000kcal)* Vegetables (serves/1000kcal)[b] Healthy Eating Index [a]	7-day physical activity recall: Physical activity
Thomson 2010 (36)	-	Food frequency questionnaire (Arizona): Energy intake [ab] Total fat (g)* Protein (g)* Carbohydrates (g)*	Arizona Activity Frequency Questionnaire: NR
Greenlee 2012 (38)	-	Food frequency questionnaire (Block):	Kaiser physical activity survey (adapted):

		Energy intake [b] Total fat (%E) Protein (%E)* Fiber (grams) Fruits & vegetables (servings) Whole grains (servings)	Household/caregiving index Active living index Sports/exercise index*
Harris 2012 (39)	-	-	-
Scott 2013 (41)	Quality of life (FACT-G and FACT-B): FACT-G* Breast subscale*	3-day diary: Energy intake Total fat (g)* Saturated fat (g)* Protein (g) Carbohydrates (g)	Fitness (8-min walking test): Predicted VO_2 max*
Single-arm trials			
McTiernan 1998 (42)	-	Food frequency questionnaire (Block): Total fat (g/d and %E)[†] Vegetables (serves/d) Fruit (serves/d)	Physical activity logs: NR
Stolley 2009 (45)	Quality of life (FACT-G, FACT-B and FACT-ES): FACT-G Breast subscale FACT-ES	Food frequency questionnaire (Block): Energy intake Total fat (g/d[†] and %E) Fiber (g/d and g/1000kcal[†]) Vegetables (serves/d)[†] Fruit (serves/d)	IPAQ (Long form): Walking Moderate activity Vigorous activity[†] Total PA

Befort 2012 (43)	Quality of Life (Breast cancer prevention trial symptom checklist) Cognitive symptom subscale Musculoskeletal subscale† Vasomotor subscale Fatigue (Brief fatigue inventory) Depression (Patient health questionnaire [PHQ-9]) Depression score† Body image (Body Image and Relationship Scale) Strength and health† Social barriers† Appearance and sexuality†	24-hour dietary recall: Energy intake† Fruit and vegetables (serves/d)† Total fat (%E)†	Minnesota Physical Activity Questionnaire: kcal/wk† min/wk†
Campbell 2012 (44)	Quality of life (FACT-B) †	3 day food records: Energy intake Total fat (g/d and %E)	Fitness (maximal graded treadmill test): VO_2 max† Metabolic equivalent (hrs/wk)†

Adverse events

Only three-of-ten RCTs (38; 39; 41) and one-of-four single-arm trials (44) reported on adverse events, with none reporting any serious adverse events. Only one study reported an adverse event directly related to the intervention (upper arm fracture) (44).

Ongoing Trials

Five ongoing trials are shown in Table 4. Two of these (SUCCESS-C and DIANA-5) are fully-powered trials evaluating the impact of a lifestyle-based, weight loss intervention on disease-free survival and breast cancer recurrence (50; 51). The LISA trial was originally designed to evaluate the effect of a lifestyle-based weight loss intervention on disease-free survival in post-menopausal women (52); however, following loss of funding, the trial recruited only 338 of the planned 2,150 participants (53). The trial will follow these participants to evaluate longer-term effects and secondary outcomes. The ENERGY trial was designed as a vanguard trial to first establish efficacy for achieving and maintaining weight loss and improvements in QOL among 693 breast cancer survivors (54). Pending successful outcomes, funding will be sought to expand to a fully-powered trial to evaluate breast cancer recurrence and disease-free survival. The CHOICE study is a non-randomized trial, evaluating the effect of two weight loss interventions (with differing macronutrient compositions) versus control group on changes in various metabolic and hormonal biomarkers (55). The SUCCESS-C, LISA and ENERGY trials are also evaluating the effect of the interventions on incidence of co-morbidities and related outcomes.

DISCUSSION

This review summarizes the intervention trial evidence on the benefits of weight loss in women with breast cancer. There is a small but growing body of evidence to suggest that

weight loss is feasible and safe in women following treatment for breast cancer. Studies have generally focused on weight loss as the primary outcome, with over half also reporting on changes in central obesity (waist circumference). However, very few studies have reported on psychosocial and treatment-related outcomes, and with the exception of fasting lipids, glucose and insulin, few have measured other cancer- and chronic disease-related biomarkers.

Table 4. Ongoing trials of weight loss interventions in women with breast cancer

Study	Sample Characteristics	Study groups	Outcomes to be assessed
SUCCESS C (50; 96-99) Germany	3642 pre & post-menopausal women Her2/neu-negative and axillary lymph node metastasis or high-risk node-negative (defined as pT ≥2, histopathological grade 3, age ≤35yrs or negative hormone receptor) early stage breast cancer; no distant disease Surgery not more than 6wks prior BMI eligibility: 24-40kg/m² for second randomization Age eligibility: ≥18yrs Recruitment via multiple cancer centers (no further details specified). Recruitment finished in 2011.	2x2 factorial design First randomization: a) 3 cycles of FEC (epirubicin, fluorouracil, cyclophosphamide) chemotherapy, followed by 3 cycles of docetaxel or b) 6 cycles of docetaxel-cyclophosphamide Second randomization (n=2292 based on BMI eligibility): a) Lifestyle intervention – Individualized, telephone, lifestyle coach-delivered intervention over 2yrs (team of nurses, dietitians, physicians, psychologists; 20 phone calls); weight loss aim of 5-10% in first 6mo followed by weight maintenance; specified energy intake (deficit of 500-1000kcal/d); 20-25% energy from fat; 150-200min/wk moderate, progressive physical activity; pedometers supplied; individual behavioral and motivational lessons; workbook provided; regularly mailed newsletters b) Control – mailed information on general health after randomization/ chemotherapy and at 1 year	Primary outcome: Disease-free survival Secondary outcomes: Obesity-related biomarkers (e.g. insulin, adiponectin, other adipokines) Genetic markers (e.g. genetic variations in germline DNA and tumor DNA) Circulating tumor cells (CTCs) Incidence of type 2 diabetes, hypertension and coronary heart disease Estimated completion: late 2016

		Follow-up planned for 5yrs	
LISA Trial (52; 53) North America	338 postmenopausal women* Stage I-IIIa breast cancer (hormone receptor positive), no recurrent or metastatic disease On adjuvant hormonal therapy with Letrozole at time of recruitment Definitive surgery within previous 3yrs BMI eligibility: 24-40kg/m² Age eligibility: not specified Exclusions include: insulin-requiring diabetes, history of other malignancies (excluding non-melanoma skin cancers) Recruited through 20 cancer centers in Canada and USA *Terminated recruitment after 338 of a planned 2150 due to loss of funding	a) Intervention – Individualized, telephone-delivered intervention over 2yrs (19 calls in total) plus manual and mailings. Weight loss aim of 10%; energy reduction (deficit of 500-1000kcal/d); 20% energy from fat; 150-200min/wk of moderate physical activity. b) Control – Mail based education only; 2yr subscription to health magazine	Primary outcome: Disease-free survival Secondary outcomes: Overall survival Distant disease-free survival Non-cancer medical events (e.g. diabetes, cardiovascular disease, arthritis) Health-related quality of life (SF-36) Biomarkers (e.g. insulin) Estimated completion: mid 2018
DIANA-5 (51; 100) Italy	1417 pre & post-menopausal women Invasive breast cancer, no distant metastasis, local recurrence or second primary breast cancer Diagnosed within previous 5 years (chemotherapy treatment completed) High risk of recurrence defined as: ER-tumor, or high serum testosterone or insulin level, or metabolic syndrome BMI eligibility: not specified	a) Intervention (Mediterranean-macrobiotic lifestyle) – Group, face-to-face sessions; 4 cooking classes and 10 meetings in first year, meetings every 2 months in year 2, every 3 months in year 3 and every 4 months in years 4-5; monthly physical activity classes in year 1. Intervention messages consistent with WCRF/AICR recommendations. 210 min/wk moderate physical activity over at	Primary outcomes: Breast Cancer recurrence (new primary, locoregional or distant recurrence) Secondary outcomes: Hormonal and metabolic biomarkers such as blood lipids, glucose, insulin, HOMA, testosterone, SHBG Biomarkers of food intake such as carotenoids, polyphenols

	Age eligibility: 35-70yrs Exclusions include: other cancer diagnoses in previous 10yrs (excluding non-melanoma skin cancer) Recruited clinics site; tumor registries; hospitals; screening units; support groups; media Recruitment completed	least 3 days; decrease sedentary behavior by 30min/d on at least 5 days; moderate calorie restriction (relative to expenditure); reduce energy density and glycemic index of foods; reduce animal protein (except fish). Print materials provided; monthly magazine b) Comparison – Leaflet with WCRF/AICR recommendations; 2-3 meetings annually	Anthropometric measures Estimated completion: not reported
CHOICE (55; 101; 102) USA	259 post-menopausal women No evidence of metastatic disease At least 4 months post-treatment BMI eligibility: 25-34.9kg/m² Exclusions include: diabetes, hepatitis B, C or HIV, cigarette smokers, weight loss ≥ 2kg in previous month Recruited through single cancer clinic	Non-randomized trial: participants allowed to choose 1 of 3 arms; a) Low carbohydrate-high fat diet – macronutrient composition 32% carb, 48% Fat, 20% Protein; deficit 500 kcal/d (in combination with physical activity and caloric intake restriction); provided with six-weeks of meal plans for specified calorie level and other supporting materials; attend up to 10 one-on-one clinic visits and 5 group visits; physical activity 10000 steps/d recommendation (provided with pedometer) b) Low fat-high carbohydrate diet – as for (a) but macronutrient composition 64% carb, 16% Fat, 20% Protein	Primary outcome: High sensitivity CRP Secondary outcomes: Other inflammatory markers (IL-6, TNF-a) Glucose homeostasis (glucose, insulin, HOMA, IGF-1, IGFBP-3, IGF-1:IGFBP-3) Cellular oxidation (8-hydroxy-deoxy-guanosine, 8-isoprostane-F2-alpha) Hormone metabolism (estradiol estrone progesterone, SHBG) Adipokines (leptin, adiponectin, ghrelin) Body composition (via BOD POD) Estimated completion: June 2012

		c) Control – general information for breast cancer patients on weight management	
ENERGY Trial (54; 103) USA	693 pre & post-menopausal women Stage I-III breast cancer diagnosed within previous 5yrs; completion of initial therapies BMI eligibility: 25-45 kg/m^2 Age eligibility: ≥21yrs Exclusions include: history of other malignancies (excluding non-melanoma skin cancer), insulin requiring diabetes Recruited through cancer registries, clinics, media and community support groups and events. Recruitment completed May 2012.	a) Intervention – Group-based, cognitive-behavioral weight loss program; weekly one-hour group sessions for 4 months, followed by fortnightly sessions for 2 months, then monthly sessions for 6 months. In addition, individual telephone and/or email contacts (10-15 mins), aiming for 14-16 contacts in year 1 and total of 24-38 calls/emails over 2yrs. Individually tailored newsletters provided quarterly from 6-24 months. Aim for 7% weight loss at 2 years; reduction in energy intake (500-1000 kcal/d deficit) via decreasing energy density; goal of at least 60min/d moderate-intensity planned exercise; strength training 2-3 times/wk; increasing lifestyle activity (10000 steps/d; pedometers provided). Provided with workbook, food and exercise journals, calories counter, digital scale b) Control (less intensive) – provided with general weight management resources and materials; individual counselling session at baseline and	Primary outcome: Weight change Secondary outcomes: Quality of life (SF-36) Assessment of co-morbidities Blood biomarkers and genetic markers (individual markers not specified) *This trial is designed as a vanguard trial. Results of this trial will inform recruitment of a larger cohort to conduct a fully powered trial to evaluated disease-free survival Estimated completion: mid 2014

		6-months (calorie level prescribed [1200-2000kcal/d]; at least 30mins/d physical activity recommended); monthly telephone call from study coordinator (standardized script to stay in touch and update details); invited to attend information sessions on healthy living every two months in year 1

Weight loss interventions that addressed a combination of diet, PA and behavior modification (considered best practice for management of overweight and obesity (56; 57)) generally achieved mean within-group weight losses ≥5% initial body weight (33; 34; 39; 43; 44), however some did not (37; 39; 45). Interventions where the PA and dietary components were more segregated (e.g., supervised exercise sessions) and with less focus on behavior modification tended to achieve less weight loss (38; 41; 42). Consistent with what has been observed in other studies (58), there is some evidence to suggest that longer interventions (>6-months) achieved greater weight loss. Similar to weight loss interventions conducted in non-cancer survivor ethnic groups (59), the three studies that targeted ethnic breast cancer survivors (37; 38; 45) achieved small mean weight losses (between 1.5-3.3% initial body weight), suggesting that more research is needed in developing interventions that are effective among minorities (59). Despite the importance of long-term weight loss maintenance (defined as maintaining weight loss for at least 12-months (60)), only two of the 14 randomized and single-arm trials assessed whether weight losses (and changes in other outcomes) were maintained after the intervention ceased, and follow-up for both were 6-months or less (38; 44).

Obesity has been postulated to influence breast cancer progression via a number of biological pathways which center on insulin, and other adipokine, inflammatory and hormonal mechanisms with significant cross-talk amongst them (48; 51; 61; 62). Recent reviews suggest that modest intentional weight loss (i.e., 5-10% body weight) can improve hormonal (e.g., estradiol) and inflammatory (e.g., CRP, TNF-a and IL-6) biomarkers (63), insulin resistance and plasma leptin concentrations (64), although these findings are based on studies

in non-cancer survivors. Effects of modest intentional weight loss on IGFs appear to be smaller and inconsistent (63) and insufficient to induce changes in total adiponectin concentrations (64; 65). Reviews on the effects of exercise-only interventions on biomarkers in a small number of trials in breast cancer survivors have shown minimal or inconsistent effects on insulin, IGFs and inflammatory markers (66-68).

The current review identified that in women following treatment for breast cancer, intentional weight loss of ≥5% was associated with reductions in insulin and leptin of 30-40%. Reductions in CRP were less consistent and changes in other inflammatory markers and adiponectin appeared unrelated to weight loss. This evidence however, is based on a small number of generally underpowered studies. A recent study by Rock et al. (69) indicated that in women diagnosed with early stage breast cancer in the previous 10 years, those who lost ≥5% of body weight, had significantly greater reductions in insulin (↓22%) and leptin (↓44%) and increases in sex hormone binding globulin (SHBG; ↑22%) than women who lost <5% of body weight over 6-months. After 18-months, the improvement in leptin concentrations was maintained, although the effect on insulin and SHBG had diminished (69). Further controlled trials in larger samples are needed to understand the influence of intentional weight loss on cancer-related biomarkers in breast cancer survivors. This research should be conducted alongside the advances in identification of biomarkers most salient to breast cancer. Also of particular relevance for breast cancer survivors, is assessment of comorbidity-related outcomes. In older breast cancer survivors, cardiovascular disease accounts for more deaths than breast cancer (70). Weight loss and lifestyle changes (increased physical activity and healthy diet) are important for reducing risk and improving management of chronic diseases such as cardiovascular disease and type 2 diabetes (22).

The negative impact of breast cancer and its treatment on psychosocial outcomes and QOL is well documented (71). Although most women return to pre-morbid functioning around 12-months post-diagnosis (72), a sizeable percentage (over 60%) experience multiple treatment-related side-effects which are reported many years after diagnosis (73). These downstream effects may be exacerbated by obesity and weight gain post-diagnosis (74; 75). Evidence from weight loss interventions in non-breast cancer survivors suggests that weight loss can improve QOL (76) and hot flashes (77). Furthermore, PA has been shown to improve many of these outcomes in breast cancer survivors (25). Weight loss may therefore be beneficial for improving psychosocial and treatment-related outcomes in breast cancer survivors, however only a small number of the studies included in this review assessed such outcomes. These studies suggest that a weight loss intervention may be beneficial for improving QOL, lymphedema, fatigue, depression, body image, joint pain and hot flashes (35; 40; 43; 44; 49). Future trials of weight loss interventions in breast cancer survivors should include a more comprehensive assessment of patient-reported outcomes. Inclusion of a control group, or more specifically an attention-control group, in future trials is important to further inform the extent to which beneficial effects on such outcomes can be attributed to weight loss versus more generic support/attention (78; 79).

No serious adverse events were reported in any of the trials included in this review. Reductions in LBM are common with weight loss (80; 81), with significant loss of LBM increasing the risk of sarcopenia and functional impairment (80; 82). Two studies (36; 44) included in this review reported significant within-group reductions in LBM after the six-month interventions. These trials evaluated diet-only interventions, with no emphasis on PA (36) or promoted aerobic exercise only (44). Resistance exercise is important for preserving LBM during weight loss (80; 82; 83) while weight bearing exercises are important for

preserving bone mineral density (BMD) (84). Obesity, in particular abdominal and visceral adiposity, are associated adversely with bone health, including lower BMD, likely as a result of the metabolic complications associated with obesity (85). Furthermore, breast cancer treatments (chemotherapy and some hormonal therapies) may induce bone loss and increase risk of osteoporosis and fractures (86). Therefore, preserving BMD during intentional weight loss is important to minimize further bone loss. No trials in this review examined changes in BMD during intervention. The evidence from this review supports the safety of weight loss in women following breast cancer treatment, but suggests that resistance and weight bearing exercise is likely to be important to prevent loss of LBM and BMD.

There are a number of limitations with the studies in this review. Many were considered to have high risk of bias. None assessed whether changes in outcomes were maintained long-term and none assessed cost-effectiveness. This evidence is important for informing decisions about resource allocation relevant to the translation and uptake of such interventions into practice (87). Furthermore, most studies recruited women a considerable time post diagnosis. There is no clear evidence on the best time to intervene regarding weight loss following a breast cancer diagnosis. Intervening early is likely to have the greatest impact on reducing morbidity and mortality from chronic diseases, such as cardiovascular disease and diabetes (88; 89), and presumably also improving breast cancer outcomes. Addressing weight loss in women closer to diagnosis and end of treatment may capitalize on the 'teachable moment' of the breast cancer diagnosis (90) for some women, whereas for others, this time is associated with high levels of distress (91). Very few studies assessed and reported on changes in diet and PA, which underpinned the weight loss interventions. Measuring changes in PA, including objective measurement via accelerometers, can be useful to determine the extent to

which improvements in outcomes, such as psychosocial indices, are due to weight loss overall, or to increases in PA independent of weight loss.

Results from the ongoing trials will provide important evidence as to the effect of weight loss on breast cancer endpoints such as disease-free survival, QOL and possible mechanisms by which weight loss improves breast cancer prognosis. A number of these studies are evaluating 'scalable' interventions that may have the potential to be translated into practice (with two evaluating interventions delivered solely via telephone). Development of interventions designed to be implemented within the context of usual care and thus mindful of resource requirements will be an increasingly important consideration for future studies. Evidence on the effectiveness of 'scalable' interventions for achieving weight loss in non-cancer survivor groups has shown: promising results for telephone delivery (92); small, inconsistent effects of web-based interventions delivered via computer (93; 94); and limited evidence to date for mobile phone SMS-based interventions (95). Testing of such interventions among cancer survivors will be an increasingly important consideration for future studies.

Table 5. Recommendations for future weight loss intervention trials in women with breast cancer

Study methodology
• Aim to recruit women closer to treatment completion and report on mean time post-diagnosis as part of baseline characteristics • Inclusion of control group; consideration of an attention control group • Improve reporting of trial outcomes in accordance with CONSORT guidelines • Power on outcomes other than anthropometric outcomes • Assess maintenance of outcomes at least 6-months after intervention completion • Assess impact of interventions on specific subgroups of breast cancer patients, e.g., those with luminal A, luminal B, and triple negative disease

Intervention • Assess the impact of multiple component interventions that include dietary energy restriction, physical activity and behavior change strategies • Interventions should include resistance and weight-bearing exercises to preserve lean body and bone mass • Further develop culturally-appropriate, ethnic-specific interventions • 'Scalable' interventions that have the potential to be translated into practice should be evaluated Outcomes Assessed • Assess and report on patient-reported outcomes (such as quality of life, fatigue, hot flashes, lymphedema etc.) and chronic disease- and cancer-related biomarkers • Assess changes in dietary intake and physical activity (including objectively measured physical activity) • Assess changes in waist circumference and body composition (including regional adiposity) to understand changes in body weight. • Assess changes in lean body mass and bone mineral density to ensure no negative effects of the intervention on these outcomes • Conduct cost-effectiveness analyses

The evidence to date on weight loss interventions in breast cancer survivors suggests that weight loss is feasible, effective (particularly multi-component interventions) and safe. Recommendations for future weight loss trials in patients following treatment for breast cancer are shown in Table 5. Ongoing trials, such as SUCCESS C, DIANA-5, ENERGY, and LISA, will provide future evidence on the benefits of purposeful weight loss on disease-free survival and QOL. Even so, continued research will be necessary to fine-tune the supportive strategies that are most effective in this patient population (and important sub-groups such as underserved minorities), and that can be implemented broadly in the context of usual care. Further trials will also help to build the evidence on the potential benefits for patients and health care costs, to assist in advocating for the provision of such programs so that they are routinely offered to overweight and obese breast cancer patients as part of their routine follow-up care.

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Table 1:

[*] Weight loss served as primary outcome

[¦] Bias score based on a 10-item checklist (refer to Tables S1 and S2)

[†] $p<0.05$ for within group change for weight and other outcomes as reported by authors (italicized indicates that this has been calculated from mean and standard deviation reported)

[‡] $p<0.05$ for between group difference for weight and other outcomes

Different superscripts indicate $p<0.05$ within group differences for other outcomes

[§] Baseline data for mean age and mean BMI is based on completers, not total randomized sample

[ǁ] Manuscript describes a 12-month intervention but only 16-week outcomes reported

[¥] Allocation to study groups not randomized

Abbreviations: %BF, percent body fat; BF, body fat; BIA, bioelectrical impedance; BMI, body mass index; DXA, Dual-energy X-ray Absorptiometry; ER+, estrogen receptor positive; FM, fat mass; HC, hip circumference; IQR, interquartile range; LBM, lean body mass; NR, not reported; ns, not significant; WC, waist circumference; WHR, waist to hip ratio.

Table 2:

[†] $p<0.05$ for within group change if reported by authors (italicised indicates that this has been calculated from mean and standard deviation reported)

***** $p<0.05$ for between group difference as reported by authors

Abbreviations: DHEA, dehydroepiandrosterone; ELISA, Enzyme-linked immunosorbent assay; HOMA-IR, homeostasis model assessment – insulin resistance; HbA1c, Glycated hemoglobin; IGF-I; Insulin-like growth factor 1; IGFBP-I; Insulin-like growth factor-binding protein 1; IGFBP-3; Insulin-like growth factor-binding protein 3; IL-6, interleukin-6; IL-8, interleukin-8; NR, not reported; RIA: radioimmunoassay; SHBG, sex hormone-binding globulin; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor

Table 3:

***** $p<0.05$ for between group differences for outcomes in randomized controlled trials

Different superscripts indicate $p<0.05$ for within group differences for outcomes for randomized controlled trials

[†] $p<0.05$ for within group differences for outcomes in single-arm trials

Abbreviations: %E, percent of total daily energy intake; CES-D, Center for Epidemiological Studies Depression Scale; FACIT, Functional Assessment of Chronic Illness Therapy; FACT-B, Functional Assessment of Cancer Therapy – Breast Cancer Subscale; FACT-ES, Functional Assessment of Cancer Therapy – Endocrine Symptoms Subscale; FACT-G, Functional Assessment of Cancer Therapy – General; IPAQ, International Physical Activity Questionnaire; NR, not reported; PA, physical activity

Table 4:

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DNA, deoxyribonucleic acid, HOMA, homeostatic model assessment; IGF-I, insulin-like growth factor-I; IGFPB-3, insulin-like growth factor binding protein-3; IL-6, interleukin-6; NR, not reported; SHBG, sex hormone binding globulin; TNF-α, tumor necrosis factor alpha; WCRF/AICR, World Cancer Research Fund/ American Institute for Cancer Research

Figure 1. PRISMA flow chart of studies through the review process