Weight Management and its Role in Breast Cancer Rehabilitation

Running title: Weight in Breast Cancer Rehabilitation

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Condensed abstract: Obesity is a risk factor for post-menopausal breast cancer, and many women diagnosed with breast cancer, irrespective of menopausal status, gain weight post diagnosis. Weight management plays an important role in rehabilitation and recovery since obesity and/or weight gain may lead to poorer quality of life, overall health and/or survival.

Abstract (170 words)

Overweight and obesity are risk factors for post-menopausal breast cancer, and many women diagnosed with breast cancer, irrespective of menopausal status, gain weight after diagnosis. Weight management plays an important role in rehabilitation and recovery since obesity and/or weight gain may lead to poorer breast cancer prognosis, as well as prevalent co-morbid conditions (e.g. cardiovascular disease and diabetes), poorer surgical outcomes (e.g., increased operating and recovery times, higher infection rates, and poorer healing), lymphedema, fatigue, functional decline, and poorer health and overall quality of life. Health care professionals should encourage weight management at all phases of the cancer care continuum as a means to potentially avoid adverse sequelae and late effects, as well as to improve overall health and possibly survival. Comprehensive approaches that involve dietary and behavior modification, and increased aerobic and strength training exercise have shown promise in either preventing weight gain or promoting weight loss, reducing biomarkers associated with inflammation and co-morbidity, and improving lifestyle behaviors, functional status, and quality of life in this high-risk patient population.

Keywords: Breast neoplasms; obesity; weight loss; diet; exercise

Introduction

Worldwide, obesity and breast cancer represent two common diseases, both with increasing prevalence,[1] and each independently having a profound impact on public health. There also is a well-established relationship between the two diseases, with most large epidemiological studies demonstrating an increased risk of developing post-menopausal breast cancer in overweight or obese women (as determined by weight, body mass index [kg/m2] or waist/hip circumference ratio).[2-6] Further, changes in weight throughout adulthood may influence breast cancer risk.[7-10] specifically, post-menopausal breast cancer risk is elevated among those who have experienced weight gain throughout adulthood, while weight loss after menopause has been associated with reduced risk. [7-10] Interestingly and in contrast to breast cancer that occurs later in life, obesity does not generally contribute to risk of breast cancer that occurs premenopause,[3-5] though interactions between age of onset, race, and BRCA mutation and subtype status are beginning to emerge and complicate these simple associations.[11;12] Given that breast cancer is a disease associated with aging with risk highest after menopause,[13] and those who are overweight or obese in their younger years are likely to remain overweight or obese as they age,[14] it is not surprising that more than one in two women diagnosed with breast cancer are overweight or obese.[15]

Weight gain following the diagnosis of breast cancer

Weight gain is common in both pre- and post-menopausal women following diagnosis.[16-19] In some of the first studies that documented weight gain more than two decades ago, weight gains of up to 11 kg. were noted in 1-out-of-4 women receiving adjuvant chemotherapy.[20;21] In more recent years; however, and as oncologists have become more aware of this prevalent side effect and have counselled patients to avoid weight gain, post-diagnosis weight gains have diminished,

but still can range up to 5.0 kgs.[22-24] Such weight gains have been demonstrated in both retrospective [25;26], and prospective studies, [18;22;24;27-36] as well as during and after a variety of adjuvant treatments, such as chemotherapy, [22;27-31;33;35] radiotherapy,[31;35] and endocrine therapy,[32] and experienced over periods as short as six months[28] and as long as 5 years [26]. Unfortunately, these weight gains also tend to be accompanied by adverse changes in body composition; specifically, gains in fat mass, particularly central fat,[22] and in the presence of either no change or declines in fat-free mass (muscle).[19;23;24;27;28;31;33;35;37] This type of weight gain has been termed sarcopenic obesity,[19;38] and has significant and adverse functional implications, such as reduced muscular strength and mobility.

Mechanisms of weight gain

The pathophysiological basis of weight gain following breast cancer remains unclear. Chemotherapy treatment has been considered a significant contributory factor through reduced metabolism as a consequence of treatment-induced ovarian failure and the subsequent rapid onset of menopause,[18] as well as reductions in physical activity post-diagnosis.[24;31;39] However, it has been suggested that with the advent of newer chemotherapeutic regimens involving shorter treatment schedules, that the incidence of weight gain following breast cancer may have declined.[23] Inconsistent relationships have been observed between weight gain following breast cancer and age, menopausal status, and/or body mass index at diagnosis.[39] Findings from population-based, prospective cohort studies are needed to help better understand the likely contributory factors to weight gain in the context of current treatment regimens and in differing breast cancer populations. Irrespective of the pathophysiologic basis, weight gain reflects an imbalance between energy intake and energy expenditure,[22] and the reasons for this imbalance

have been explored. There is some evidence to support declines in total energy expenditure, by reductions in resting energy expenditure [22;27] and/or reductions in energy expenditure attributed to physical activity [27;31] during and following treatment. Mixed findings have been observed for energy intake, with some studies showing declines,[27] while others show energy intake remains unchanged;[31;35] few studies however provide data showing that caloric consumption increases over baseline levels.

Implications of overweight and obesity and/or weight gain at diagnosis and throughout the course of survivorship on disease-free and overall survival

Upon diagnosis, being overweight or obese elevates risk (up to 4-fold) of developing multiple other diseases such as type II diabetes, asthma, chronic back pain, osteoarthritis, and cardiovascular disease,[40;41] and this risk may be elevated further as a consequence of receiving treatment.[18;42;43] In fact, women with breast cancer are just as likely, if not more, to die from heart disease as their breast cancer.[40;44] Results from a recent meta-analysis also demonstrate that obesity is associated with poorer overall and breast cancer-specific survival.[45] The meta-analysis included results from 43 studies which enrolled women diagnosed with breast cancer between 1963 and 2005, with sample sizes ranging from 100 to 424,168. Results show that obese women are at higher risk of all-cause (HR=1.33, 95% CI: 1.21, 1.47) and breast cancer specific (HR=1.33, 95% CI: 1.19, 1.50) mortality when compared to non-obese women with breast cancer. Moreover, differentials in rates of survival have varied, and have appeared to be dependent on the following factors (though it should be noted that some of these confidence intervals overlap): 1) index of obesity used, e.g., BMI (HR=1.33; 1.23, 1.44) versus waist-hip ratio (HR=1.31; 1.14, 1.50); 2) menopausal status, e.g., pre-menopausal (HR-1.47; 1.19, 1.83)

versus post-menopausal (HR=1.22; 0.95, 1.57); 3) diagnosis date, e.g., before 1995 (HR=1.31; 1.16, 1.46) versus afterward (HR=1.49; 1.31, 1.68); and 4) study mode, i.e., data from treatment (HR=1.22; 1.14, 1.31) versus observational (HR=1.36; 1.23, 1.44) studies.

Studies of the prognostic consequences of weight change post-diagnosis have yielded inconsistent findings. Some studies have shown increased rates of recurrence, as well as disease-specific and all-cause mortality;[20;34;46;47] whereas others have not observed such relationships.[26;48;48;49] Moreover, j-shaped curves as originally reported by Goodwin et al,[17] which show increased disease-specific mortality with BMI, have been supported by the recent findings of Nichols et al.[47] Chen et al.[50]and Thivat et al.[46] Such findings support the need for weight management strategies post –diagnosis.[40]

While speculation exists that weight loss following a diagnosis may lead to survival benefits among women who are overweight,[45;51] there has yet to be a prospective study to answer this research question. However, an NIH-funded vanguard trial entitled, ENERGY trial (Exercise and Nutrition to Enhance Recovery and Good Health in You), is underway to explore the feasibility of this approach and to obtain precision estimates for a larger study. Given that overweight and obese breast cancer survivors are more likely, at the point of diagnosis, to have diabetes and cardiovascular disease, as well as other obesity-related conditions, such as osteoarthritis, or gallbladder and gastro-esophageal reflux disease or are more likely to develop some of these problems (e.g., cardiovascular disease) as late effects, the benefits of weight control are obvious. Indeed, these are conditions for which there is proven benefit of weight management. Thus, it is of paramount importance to encourage breast cancer survivors to achieve and maintain a weight that is within the ideal range in an effort to promote overall health.[40]

The influence of obesity on specific comorbidities, acute symptoms and late effects

In addition to cardiovascular disease and diabetes, which top the list as prevalent and serious health concerns for breast cancer survivors, and which can impede progress to full recovery, there are several other conditions and treatment-associated sequelae (see below). These also are conditions for which obesity has been linked to adverse outcomes. While weight management is likely to offer a means to reduce these risks, at present no data exists to definitely support this approach.

Surgical Risk

Surgery is the mainstay of breast cancer treatment, and is either performed as the initial form of curative treatment, or performed after neoadjuvant therapy. While obesity does not have a significant impact on some of the surgeries for breast cancer that are relatively minor and conducted on an outpatient basis (e.g., lumpectomy), it can have adverse consequences on more involved procedures. Mastectomy and axillary node dissection, and especially reconstructive surgery can result in poorer surgical outcomes if the patient is obese. Since 33-54% of women receive reconstructive surgery either during or after curative procedures, this is a prevalent concern.[52] Obesity has long been acknowledged as contributing to increased operating and recovery times, more blood loss, poorer healing, and higher infection rates not only for surgery in general, [53-55] but also surgeries that specifically involve the breast. [56-58] Most recently, Chen et al.[56] reported an almost 12-fold increase in the complication rate among obese vs. non-obese patients.

Lymphedema

The risk of lymphedema after breast cancer surgery has been chronicled over several decades,[59] and the results of four large cohort studies consistently show higher risk among women who are obese (BMI ≥ 30).[60-63] Weight gain occurring after diagnosis has also been suggested as a risk factor.[64] In a recent prospective cohort of 138 newly diagnosed breast cancer survivors, Ridner et al.[63] examined the impact of post-operative weight gain on the incidence of lymphedema. Pre-operative arm-volume was measured by perometer, with quarterly post-surgical follow-up. At 30 months, 27 women (19.6% of sample) had developed lymphedema and this number did not differ by weight status using either criterion for lymphedema (i.e., 200 milliliter difference from baseline or 10 percent increase in arm volume). Those who had a BMI ≥ 30 at baseline had a higher risk of developing lymphedema (odds ratio = 3.59; 95% CI = 1.42-9.04). However, a general increase in BMI from baseline or increase in BMI to ≥ 30 at 30-months post-surgery was not associated with an increased risk of lymphedema. Since most of the sample was overweight or obese prior to surgery, it is unknown whether increases in weight status among normal weight women would yield similar findings. Further, findings from several prospective cohort studies have demonstrated no relationship between higher body mass index and lymphedema risk. Nonetheless, higher body mass index has never been associated with reduced risk and the importance of maintaining healthy body weight in relation to other breast cancer outcomes is clear.[65-67]

Further evidence for the role of body weight on lymphedema is provided by a single 12-week intervention study with 24 breast cancer survivors. The weight loss intervention (individual dietary advice to produce a two pound per week weight loss) was aimed at producing a significant reduction in upper extremity lymphedema volume, calculated from arm

circumference measures. Compared to the control group, women in the intervention group lost on average 3.3 kg and had a significant reduction in swollen arm volume on the affected side.[68]

Fatigue

While fatigue is reported as a longstanding and well-documented issue among women with breast cancer, only recently have associations between body weight and fatigue been investigated. In several cross-sectional studies that range from 9 months to 18 years post-diagnosis, women who were overweight and obese, or those who gained weight post-diagnosis were more likely to report fatigue.[62;69-71] In a recent longitudinal study of 304 early stage breast cancer survivors, women who were obese prior to the start of adjuvant treatment were more likely to develop cancer-related fatigue at 42-months post-treatment than those with BMIs < 30.[72] In a small cross-sectional study of older breast cancer survivors, higher body fat, as measured by dual-energy x-ray absorptiometry also was significantly and positively associated with higher levels of fatigue.

Arthralgias

While obesity is strongly linked to the development of osteoarthritis and joint pain in non-cancer survivors,[73] information on the impact of obesity on arthralgia or joint pain secondary to breast cancer is limited and conflicting. Mao et al. [74] found no association between BMI and arthralgia in a cross-sectional study of 300 postmenopausal breast cancer survivors, whereas in a sample of 200 postmenopausal women receiving adjuvant aromatase inhibitors (AI) for early stage breast cancer, Crew et al. [75] found that 34% of overweight women (BMI 25-30) reported AI-related joint pain and stiffness compared to 57% of normal weight (BMI <25) and 54% of

obese (BMI >30) patients. In contrast, the largest study conducted to date (9366 postmenopausal breast cancer survivors randomized to anastrozole or tamoxifen), Sestak et al.[76] found more joint symptoms in obese women compared to those who were overweight or normal weight.

Bone Health

In contrast to several other health conditions for which overweight and obesity serve as risk factors, for bone health a higher BMI is consistently associated with higher bone mineral density and a decreased risk of fracture.[77-79] Indeed, a low BMI (< 20) is one of eight fracture risk factors for breast cancer survivors identified in a systematic review by Hadji et al.[80] Thus, weight loss pursuits by women who have had breast cancer should be to seek BMI within the healthy weight range (BMI 20-25) and not below 20. Most importantly, weight bearing exercise plays an integral role in weight loss programs and should be included to ensure preservation of bone mass as body weight declines.[81;82]

Other Sequelae of Breast Cancer and its Treatment

In addition to the sequelae listed above, women who have been treated for breast cancer either with chemotherapy or hormonal therapy often experience vasomotor symptoms (i.e., hot flashes) that significantly reduce their quality of life. A recent study by Su et al.[83] among 300 breast cancer survivors, found that among those who gained more than 10 pounds post-diagnosis (roughly a third of the sample), the risk of hot flashes, as well as increased severity of hot flashes was more than double that of those who were weight stable. While the utility of both regular exercise and weight loss has been suggested for the treatment of this prevalent side effect, consensus has yet to be achieved and more research is needed.[84;85] As noted in the beginning of

this section, cardiovascular disease and diabetes are prevalent co-morbidities for which breast cancer patients, particularly overweight or obese women, are at greater risk.[40] These comorbidities may be present at the time of diagnosis, but these diseases oftentimes appear afterwards, particularly since they are weight dependent and weight gain is common. Currently, it is difficult to disentangle whether downstream sequelae, such as peripheral neuropathy (seen also with uncontrolled diabetes), exacerbates chemotherapy-induced peripheral neuropathy, or if these events are totally independent. Similarly, it is difficult to ascertain whether underlying and uncontrolled cardiovascular disease contributes to chemotherapy-induced cardiotoxicity. Given that the study of cancer survivorship is relatively new, at this juncture it is unknown whether overweight and obesity contribute independently to the sequelae of breast cancer treatment, or whether these events are mediated primarily by these other diseases.[64;86] Since weight management is a key and proven therapy for both diabetes and cardiovascular disease, it is speculated that if these conditions are controlled, it also may help prevent downstream morbidity.

Weight Management:

Two organizations (the American Cancer Society [ACS] and the World Cancer Research Fund- American Institute of Cancer Research [WCRF-AICR]) provide diet and exercise guidelines for cancer survivors; at the forefront of each set of guidelines is the recommendation for weight control.[40;87] These guidelines emanate from the growing body of research just reviewed that suggests that obesity is a poor prognostic factor for cancer, as well as the overwhelming evidence that weight control is important for managing prevalent co-morbid conditions. Currently, it is suggested that until more is known, the strategies endorsed for weight

management in normal populations be applied to cancer survivors.[40] Thus, interventions that bank on a three-part approach of diet, exercise and behavioral therapy are recommended.[88] Women who are normal weight at diagnosis should be apprised of the risk of weight gain, and encouraged to consume diets which are nutrient-dense, but limited in the amounts of simple sugars and added fats which increase caloric load, as well as to pursue aerobic and strength training exercises (to burn energy and avoid sarcopenia).[38;40;87] For women who are overweight or obese these strategies also can be pursued to avoid additional weight gain; however more structured approaches may be necessary if weight loss is the goal.[89] Indeed, moderate weight loss of up to two pounds per week can be pursued safely at any time post-diagnosis, assuming that women are appropriately monitored and approval is given by the oncology care physician.[40] Many women with breast cancer however elect to delay concerted efforts toward weight loss until active treatment is complete.

Several interventions to avoid increased adiposity and adverse, treatment-associated changes in body composition,[90-93] as well as to promote weight loss among overweight and obese women with breast cancer have been tested over the past two decades and are summarized in Table 1.[94-102] These trials have been conducted among women at various stages in the cancer care continuum, from those who are newly diagnosed and actively receiving treatment to those who are long-term cancer survivors, and in samples that are as small as 10 to as large as 289. Overall, these studies have shown success, with greater improvements in body weight status resulting from interventions that use multicomponent approaches involving diet, physical activity and behavior modification. For example, in the trial by Loprinzi et al.[91] in which dietary restriction was pursued without a physical activity component, there were negligible differences between the intervention and control groups, whereas the multicomponent interventions of

Goodwin et al.[93] and Mefferd et al.[94] resulted in greater weight loss and differences between the intervention and control arms. While the magnitude of weight loss may appear greater with clinic-based interventions, it is difficult to disentangle whether such interventions are actually superior or whether these trials attract self-selected samples that are more motivated to adhere to weight loss regimens. An example of this discrepancy is provided by the two feasibility studies of Demark-Wahnefried et al.[90;92] in which a clinic-based study resulted in improvements in body composition that appeared far superior to those with a home-based program. However, the clinic-based program was successful in only accruing highly motivated, upper socio-economic women who were willing to attend thrice weekly exercise sessions (and who tended to have higher physical activity levels at baseline),[92] whereas the home-based program attracted a diverse group of women who were exercisers and non-exercisers alike.[90] In general, however, most of these trials show improvements in body weight or body composition status, and also improvements in diet and physical activity behaviors, various biomarkers (e.g., serum lipids, cytokines and adipokines), and clinical outcomes (e.g., quality of life and physical functioning). More study is needed to discern the optimal timing of interventions, sequencing of behavioral components, and the impact of weight loss on breast-specific and overall health outcomes, as well as health care costs.

The need for prospective surveillance of body weight (prospective model)

As highlighted earlier, the majority of women diagnosed with breast cancer are overweight or obese at diagnosis, and all women (irrespective of baseline weight) are at risk of weight gain post-diagnosis. Thus, there is a real need to educate women about the potential implications of weight and weight gain on disease and treatment outcomes, as well as adverse effects. Regular

prospective surveillance, commencing pre-treatment, as suggested by the prospective surveillance model described by others in this supplement issue of Cancer, is the key to initiating relevant discussions around body weight. Body weight, and ideally more direct measures of body fat afforded by anthropometrics, bioelectric impedance, or other testing, should be objectively measured at clinical visits to ensure women have an accurate representation of their body weight and to demonstrate that weight is an outcome of interest to their health care team. All women, regardless of initial BMI, should be provided with information on weight management strategies during treatment Regular assessment, suggested monthly and/or during each routine follow-up visit until treatment cessation, will enable identification of those women experiencing steady or rapid weight gain, as well as those women already overweight or obese who are not achieving weight loss. Such regular measurement will allow for additional, early and individualized, intervention as needed, likely reducing the extent of weight gains and optimizing the ability for weight loss. For women who are overweight or obese (BMI > 25), weight maintenance or weight loss strategies during adjuvant or following adjuvant treatment should be encouraged, with the goal of weight loss toward achieving a healthy body weight by 2 years post-adjuvant treatment. Furthermore, the integration of regular weight-bearing and strength exercises into these strategies is crucial for optimizing muscle mass and preserving bone health. Importantly, it is clear that there are many contributing factors to a woman's weight at diagnosis and weight gain post-diagnosis. Therefore, weight should be considered an important outcome to measure throughout and beyond all forms of breast cancer treatment, rather than be viewed as an outcome of interest for specific subgroups of women based on treatment choices or patient characteristics.

Summary

It can be expected that higher proportions of women will be overweight or obese at the point of diagnosis as the worldwide pandemic of obesity spreads.[41] As such it is of paramount importance that health care messages to avoid weight gain during adulthood as a means of cancer prevention (particularly among high risk women) be disseminated. While it is currently unknown whether post-diagnosis weight loss can improve prognosis and disease-free survival, evidence suggests that weight management is key to controlling prevalent co-morbid conditions in this patient population. Thus, health care professionals should encourage weight management at all phases of the cancer care continuum as a means to avoid adverse sequelae and late effects, and improve overall health.

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Table 1: Intervention studies specifically directed toward weight management or weight loss in women with breast cancer

Authors	Sample	Design	Intervention	Frequency/duration	Results
Prevention of weight gain or gains in adiposity					
Loprinzi et al. 1996 [85]	107 Premenopausal patients actively receiving adjuvant chemotherapy.	2-arm (initial oncologist advice vs. regular dietician counseling) Randomized Control Trial (RCT)	Individual dietician counseling to maintain weight. No reported theory.	Monthly for 6 months	Median weight changes at 6 month follow-up were 2.0 kg in the experimental group vs. 3.5 kg in the control group (N.S.). The median changes in average calorie consumption were reductions of 120 vs. 46 kcal/day on weekdays & 196 versus 20 kcal/day on weekends for the experimental & control groups, respectively
Demark-Wahnefried et al. 2002. [86]	10 Premenopausal, stage I & II breast cancer patients actively receiving adjuvant chemotherapy. Mean age 42, 100% Caucasian	Single arm feasibility study compared to historic controls	Clinic-based aerobic & strength training exercise + healthy diet (<20% kcal from fat, 5+ serving fruits & vegetables/day, & 1,200-2,500 mg. calcium/day). Social Cognitive Theory.	Thrice weekly, graduated intensity individual sessions for 6-months	Compared to historic controls, intervention participants experienced the following changes in body composition: Total body mass +2.2 (0.4) vs. -2.0 (1.3) kg. (p=.02); % Body fat: +1.8 (1.6) vs. -1.3 (1.2) (p=.002); Fat mass: +2.0 (0.3) vs. -1.2 (1.5) kg. (p=.04); & Lean body mass: -0.3 (.01) vs. +0.1 (1.5) kg. (N.S.). Attrition 10%.
Demark-Wahnefried et al. 2008. [84]	90 newly diagnosed premenopausal women with Stage I-IIIA breast cancer actively receiving adjuvant chemotherapy. Mean age = 41.8.	3-arm feasibility trial	Mailed materials & telephone counseling. All 3 arms counseled on 1,200-1,500 mg of calcium/day. Arms 2 & 3 received exercise counseling promoting aerobic exercise (≥30 minutes/day at least 3 days/week) & resistance training for legs & lower body. Arm 3 also received counseling on diet with <20% of kcal from fat & at least 5 daily servings of fruits & vegetables. Social Cognitive Theory + Health Belief Model.	All participants received written mailed materials & telephone counseling (14 sessions over the 6 month study period).	Measures of adiposity were generally lower in the study arm that received all intervention elements (diet + exercise), though the only significant difference was in extremity adiposity, i.e., 0.7% vs. 1.2% vs. 0.1%, in control vs. exercise alone vs. exercise + diet arms, respectively (p=.047). Fat and fruit & vegetable change scores differed significantly in the diet + exercise arm; though no differences in change scores were observed for physical activity. No differences between study arms were observed for quality of life, anxiety, depression, serum lipids, sex hormone binding globulin, insulin, proinsulin, C-reactive protein, interleukin-1B, or tumor necrosis factor receptor- II. Targeted accrual was achieved with 8.8% drop-out.
Djuric et al. [102]	40 newly diagnosed adult women (over age	2-arm feasibility	The Written Material Group received a My Pyramid Plan	The Written Material Group received	The telephone counseling arm reported significant improvements in physical activity over the time

	18) with Stage I-IIIA breast cancer either scheduled or within 2 weeks of initiating chemotherapy. Mean age = 52.2	trial	and brochures on diet and exercise from the American Cancer Society. The Telephone Counseling Group received Written Materials and Instruction by a Registered Dietitian who used concepts from Social Cognitive Theory and Motivational Interviewing	materials through the mail; the Telephone Counseling Group received variable contact weekly initially and then monthly toward the end of the 12 month study period (19 contacts in total)	period; no such effects were observed in the written material group (between group differences were not presented). Few differences existed in measures of adiposity and no differences were observed in blood pressure or biomarkers (insulin, leptin, C-reactive protein, C-peptide, glucose, or carotenoids) over time in either of the groups. Targeted accrual was achieved with 25% drop-out.
Prevention of weight gain and promotion of weight loss					
Goodwin et al. 1998.[87]	61 women with newly diagnosed locoregional breast cancer (BMI= 20-35), 100% Caucasian	1-arm Phase II trial	Multicomponent intervention that intervened on diet, aerobic physical activity & behavior modification. Normal weight women received guidance on weight maintenance whereas overweight & obese women received instruction on weight loss	Weekly for 10 weeks & monthly for the remainder of the 1-year study period	Mean weight loss was 0.53 ± 3.72 kg. Weight loss was greatest in initially overweight women (-1.63 ± 4.11 kg & in those not receiving chemotherapy (-2.15 ±2.83 kg). 70.9% met predefined criteria for success. Aerobic exercise increased significantly during the intervention ($p = 0.00005$) & was the strongest predictor of success (OR 1.73 for each additional 30 minutes of exercise weekly, $p = 0.003$). Changes in caloric intake were not significant, but fat intake decreased, & fibre & carbohydrate intake increased significantly. Eating behavior & psychological status improved significantly. 10% attrition
Promotion of weight loss					
de Waard et al. 1993.[89]	102 Obese post-menopausal breast cancer patients who had newly completed radiation therapy. 100% Caucasian.	2 arm (intervention vs. usual care) feasibility RCT in 5 hospitals in Poland &the Netherlands	Individual dietary & behavior modification counseling	Initial counseling with variable follow-up for a 1-year period	At 1-year follow-up the median weight loss was 6 kg in the experimental arm. Further follow-up in the Netherlands at 3 years suggested that this weight loss was durable. This trial began as a fully-powered RCT to test the impact of weight loss as an adjuvant therapy, but was downgraded to a feasibility trial due to recruitment issues (oncologists failed to acknowledge weight control as an issue) & the introduction of Tamoxifen.
Djuric et al. 2002.[90]	48 Breast cancer survivors (BMI = 30-44). 73% Caucasian, mean age 51.7 years.	Pilot 4-armed RCT (+/- individualized approach +/- Weight Watchers®	The intervention relied heavily on dietary counseling with some behavior modification. The Weight Watcher® arms encouraged physical activity.	Variable contact throughout the 1-year study period with weekly contact in those assigned to Weight Watchers®. Individualized dietician contact was weekly for the 1st 3	Weight change (mean $\pm$ SD) after 12 months was as follows: +0.85 $\pm$ 6.0 kg in the control group, -2.6 $\pm$ 5.9 kg in the Weight Watchers® group, -8.0 $\pm$ 5.5 kg in the individualized group, and -9.4 $\pm$ 8.6 kg in the group receiving both . Weight loss was significantly related to frequency of attendance & attendance was more frequent in the group receiving both interventions. Secondary analyses by Jen et al.[91] found significantly decreased levels

				months, biweekly for months 3 to 6, & monthly thereafter.	of leptin & cholesterol in the comprehensive group.
Mefferd et al. 2006.[88]	85 Overweight or obese breast cancer survivors diagnosed with stage I-IIIa breast cancer within 14 years. Mean age 56 years, 93% Caucausian.	2-arm (experimental vs. usual care) RCT	Multi-component weight management intervention involving dietary, exercise, behavior modification & cognitive restructuring.	Weekly group classes for 4 months supplemented with telephone counseling	% Change in body weight was -0.6% vs. -6.8% in the usual care & experimental arms, respectively. Significantly greater decreases were observed in the experimental arm in BMI, waist & hip circumferences, & total body & % body fat. No differences were noted in lean body mass. Attrition rate 11%. Secondary analysis by Pakiz et al.[92] suggests significantly decreased TNFα levels in the intervention arm & a trend toward lower IL-6.
Shaw et al.[64]	24 Breast cancer survivors at least 12 months out from curative treatment with documented lymphedema. Median age 60.	RCT with assignment to a booklet on healthy eating (attention control) or dietary intervention,	Dietitian delivered weight loss intervention that promoted a restriction in kcal intake of 1,000 kcal/day. Dietary intake was monitored.	12-week intervention	A decrease in weight of 3.3 $\pm$ 2.6 kg was observed in the intervention group compared to 0 $\pm$ 2.97 in the control group. Significant decreases were also observed in BMI, kcal intake & fat intakes. There was a significant difference in excess arm volume between the control group & the weight reduction Group (P <.003).12.5% attrition.
Djuric et al. 2009.[93]	24 African American breast cancer (Stages I-IIIA) survivors. BMI 30-45. Mean age=55.	Feasibility study of diet counseling vs. diet + spirituality counseling.	Weight Watchers® approach +/-spirituality counseling (12-step approach	Weekly classes for the 1st 3 months, biweekly sessions 3-6 months & monthly sessions for remainder of 18 month program.	No between arm differences in weight, but significantly greater improvements in vegetable intake (p=.013) & spirituality (p=.024) in the Diet + Spirituality arm. 8% attrition.
Stolley et al. 2009.[94]	23 African American breast cancer survivors, mean age 51.	1-arm feasibility trial	Multicomponent weight loss intervention that included tailored dietary, physical activity & behavioral instruction. Social Cognitive Theory & Health Belief Model.	Twice weekly classes for 6 months.	A significant (p<.001) decrease was observed in weight (mean change −5.57 (−8.63 to −2.51) pounds, with a corresponding decrease in BMI. A significant decrease in dietary fat & increases in dietary fiber & vegetable intakes, as well as an increase in vigorous physical activity was observed. 13% attrition
Morey et al. 2009.[95]	641 older, overweight, long-term survivors of breast (n=289), prostate (n=261), and colorectal (n=91)	2-arm RCT Diet-exercise intervention vs. wait list control.	Telephone counseling & mailed print material-based diet & exercise intervention based on Social Cognitive Theory & the Trans-theoretical	12 month intervention (personally-tailored workbook & quarterly newsletters, 15	Weight loss was greater (2.06 kg for intervention vs. .92 kg for control, p<.001). At 12 months, physical function declined less rapidly in the intervention arm (−2.15; 95% confidence interval [CI], −0.36 to −3.93), compared to the control arm (−4.84; 95% CI, −3.04 to −6.63) (p=.03).

	cancer. Mean age=73. Mean years since diagnosis=9. 89% Caucasian.		Model. Goals set at 15 minutes strength training every other day, 30 minutes/day endurance exercise, 7-9 servings/day fruits & vegetables, reduce fat to 10% of energy intake, 10% weight loss.	telephone sessions (lasting 15-30 minutes) & 8 prompts).	Physical activity, dietary behaviors, & overall quality of life improved significantly in the intervention group, compared with control. 13% attrition.