Obesity and Breast Cancer: Risk, Outcomes, and Future Considerations

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Abstract: The proportion of adults who are obese has increased dramatically in the United States over the last 30 years. Obesity has been linked to an increased risk of developing a number of malignancies, including postmenopausal breast cancer. Evidence also suggests that obesity at the time of breast cancer diagnosis is linked to an increased risk of breast cancer–specific and overall mortality in both premenopausal and postmenopausal women with early-stage breast cancer. Obesity is linked to an increased risk of secondary malignancies in women with early breast cancer, and studies suggest that weight gain after diagnosis increases overall mortality. Despite the data linking obesity to poor outcomes in women with early breast cancer, there are currently no data from randomized trials testing the impact of weight loss on breast cancer outcomes. A number of recent randomized controlled trials have shown that weight loss interventions are feasible in obese survivors of breast cancer, yielding loss of 5% to 6% of body weight, and several ongoing randomized phase 3 clinical trials are evaluating the effect of weight loss interventions on breast cancer outcomes. These studies will help define the role of weight loss in the management of obese women with early breast cancer.

Introduction

Breast cancer is the most common cancer in women in the United States and worldwide. Nearly 250,000 cases of breast cancer are diagnosed each year in the United States, and approximately 40,000 deaths occur.[1] Studies have demonstrated that obesity is linked to an increased risk of developing and dying of breast cancer. Rates of obesity are rising dramatically in the United States and worldwide, potentially compromising efforts to reduce breast cancer incidence and improve outcomes. In this article, we examine the evidence supporting the links between obesity and breast cancer incidence and prognosis, review the weight loss intervention studies in breast cancer populations, and preview the ongoing trials evaluating the effect of intentional weight loss on breast cancer outcomes.

Obesity and Breast Cancer Risk

A number of meta-analyses have evaluated the relationship between obesity in postmenopausal women and the risk of developing breast

Table 1. Selected Studies Evaluating Breast Cancer Risk and Obesity

	Studies/Number of Women/Study Types	Results		General Comments
		Premenopausal (95% CI)	Postmenopausal (95% CI)	
Renehan,[2] 2008	• 34 studies • Sample size: 2,559,829 • Cohort, case-control, and control arms from clinical trials	*Per 5-point increase in BMI:* • RR, 0.92 (0.88-0.97)	*Per 5-point increase in BMI:* • RR, 1.12 (1.08-1.16)	Meta-analysis of BMI and incidence of cancer
Munsell,[3] 2014	• 89 studies • Meta-analysis of case-control and cohort studies through 2012	• RR, 0.83 (0.75-0.91) • HR+: RR, 0.78 (0.67-0.92) • HR–: RR, 1.06 (0.70-1.60)	• RR, 1.18 (1.12-1.25) • HR+: RR, 1.39 (1.14-1.70) • HR–: RR, 0.98 (0.78-1.22) • HRT+: RR, 1.18 (0.98-1.42) • HRT–: RR, 1.42 (1.3-1.55)	Meta-analysis of BMI and BC risk according to HRT and HR status
Neuhouser,[5] 2015	• Prospective observational study • 67142 women and 3388 cancers	–	• HR, 1.37 (1.23-1.53) • HR+: HR, 1.52 (1.33-1.74) • HR–: HR, 1.15 (0.84-1.57) • HRT: no effect	Secondary analysis of Women's Health Initiative
Bandera,[6] 2015	• 4 studies • Combined case-control study with 12060 controls and 3174 cancers	*BMI ≥35 vs <25:* • OR, 0.83 (0.66-1.05) • HR+: OR, 0.81 (0.61-1.07) • HR–: OR, 1.13 (0.71-1.80) *Young Adult BMI ≥30 vs 20-24.9:* • OR, 0.77 (0.55-1.07) • HR+: OR, 0.65 (0.42-0.99) • HR–: OR, 1.08 (0.60-1.95)	*BMI ≥35 vs <25:* • OR, 1.08 (0.88-1.34) • HR+: OR, 1.31 (1.02-1.67) • HR–: OR, 0.75 (0.54-1.04)	Exclusively African American women
Keum,[4] 2015	• 10 studies • 4570 cases of BC • Meta-analysis of prospective observational studies through 2014	*Per 5-kg increase in weight:* • RR, 0.99 (0.95-1.03)	*Per 5-kg increase in weight:* • RR, 1.11 (1.08-1.13) • HRT+: RR, 1.01 (0.99-1.02) • HRT–: RR, 1.11 (1.08-1.13)	Risk of cancer incidence and adult weight gain, defined as weight from early adulthood (18-25 years) to study enrollment

BC, breast cancer; BMI, body mass index; HR, hazard ratio; HR+, hormone receptor–positive breast cancer; HR–, hormone receptor–negative breast cancer; HRT+, women who took hormone replacement therapy; HRT–, women who did not take hormone replacement therapy; RR, risk ratio. Risk is given for BMI ≥30 vs <25 unless otherwise stated.

cancer (Table 1). Renehan and colleagues in 2008 analyzed 31 studies and found a 12% increase in the risk of developing breast cancer for each 5-point increase in body mass index (BMI) (relative risk [RR], 1.12; 95% CI, 1.08-1.16).[2] In 2014, Munsell and colleagues evaluated 39 studies (moderate but incomplete overlap with the Renehan analysis) and found that patients who were obese (BMI ≥30) had an 18% increase in the risk of breast cancer compared with women of normal weight (BMI <25) (RR, 1.18, 95% CI, 1.12-1.25).[3] In a third meta-analysis,

Keum and colleagues demonstrated that adult weight gain was also linked to an increased risk of breast cancer.[4] In this analysis of 7 prospective cohort studies, they found a RR of breast cancer of 1.11 (95% CI, 1.08-1.13) per 5-kg increase in adult weight gain (defined as weight gain from early adulthood to study enrollment).

Most reports have suggested that obesity is associated with an increase in hormone receptor–positive postmenopausal breast cancer, but not in hormone receptor–negative disease. In the Munsell meta-analysis, there was a

39% increase in the risk of hormone receptor–positive breast cancer in obese vs normal-weight women (95% CI, 1.14-1.70), but no increase in the risk of hormone receptor–negative cancers (RR, 0.98; 95% CI, 0.78-1.22).[3] Similar findings also were seen in 2 more recent studies. A secondary analysis of the Women's Health Initiative demonstrated a 52% increase in the risk of hormone receptor–positive breast cancer in obese vs normal-weight women (hazard ratio [HR], 1.52; 95% CI, 1.33-1.74), but no significant increase in the risk of hormone receptor–negative cancers (HR, 1.15; 95% CI, 0.84-1.57).[5] A compiled evaluation of 4 case-control cohorts of African American women, including 2025 cases of postmenopausal breast cancer, also showed similar results; women whose BMI was 35 or greater had a 31% increase in the risk of hormone receptor–positive breast cancer compared with women of normal weight (odds ratio [OR], 1.31; 95% CI, 1.02-1.67).[6] There was no difference seen in the risk of developing a hormone receptor–negative breast cancer (OR, 0.75; 95% CI, 0.54-1.04) in women whose BMI was 35 or greater. In this cohort, women with a BMI of 35 or greater had a lower risk of developing a triple-negative breast cancer compared with normal-weight women (OR, 0.60; 95% CI, 0.39-0.93).

The association between obesity and increased postmenopausal breast cancer incidence appears isolated to women who have not taken hormone replacement therapy (HRT), which itself is a risk factor for breast cancer. In a subset analysis of the Munsell meta-analysis that evaluated 5 studies with available data on HRT use and included 7048 cases of breast cancer, obesity was associated with a 42% increased risk of breast cancer among those who had never taken HRT (RR, 1.42; 95% CI, 1.3-1.55) and no increase in risk of breast cancer for women taking HRT (RR, 1.18, 0.98-1.42).[3] Similarly, Keum and colleagues found that adult weight gain was associated with an 11% increase in risk of breast cancer in women who had never taken HRT (RR, 1.11; 95% CI, 1.08-1.13) for every 5 kg of weight gain and no increase in risk for those who had taken HRT (RR, 1.01; 95% CI, 0.99-1.02).[4]

Studies have shown that obese premenopausal women are at slightly lower risk of developing breast cancer compared with their normal-weight counterparts. Renehan and colleagues analyzed 20 cohort and case-control studies and found an 8% decrease (RR, 0.92; 95% CI, 0.88-0.97) in the risk of premenopausal breast cancer for every 5-point increase in BMI.[2] In another analysis of 16 case-control studies not included in the Renehan analysis, there was similarly a small but significant decrease in risk of premenopausal breast cancer in obese vs normal-weight women (RR, 0.83; 95% CI, 0.75-0.91).[3] This decrease in risk of premenopausal breast cancer in obese women was seen for hormone receptor–positive disease (RR, 0.78; 95% CI, 0.67-0.92) but not for hormone

receptor–negative breast cancer (RR, 1.06; 95% CI, 0.70-1.60). In a third case-control study that included 1149 cases of premenopausal breast cancer not included in the prior meta-analyses, historical obesity (measured as young adult weight) was associated with a decreased risk of hormone receptor–positive breast cancer (OR, 0.65; 95% CI, 0.42-0.99), but not overall breast cancer (OR, 0.77; 95% CI, 0.55-1.07) or hormone receptor–negative breast cancer (OR, 1.08; 95% CI, 0.60-1.95).[6]

It is not well understood why obesity is associated with an increased risk of postmenopausal hormone receptor–positive breast cancer but a decrease in the risk of premenopausal hormone receptor–positive breast cancer. One leading hypothesis for the pathophysiology relating obesity to breast cancer risk focuses on the differential impact of obesity on sex hormone levels in premenopausal and postmenopausal women. Postmenopausal women derive estradiol from peripheral conversion of androgens by the enzyme aromatase. Adipose tissue is rich in aromatase, which results in obese women having higher levels of estradiol.[7,8] This may also explain the lack of elevated risk in the subset of obese postmenopausal women receiving HRT, where their risk is dominated by the excess risk from these exogenous hormones. In contrast to obese postmenopausal women, obese premenopausal women have a reduced breast cancer risk. Obesity can be related to anovulation, which has been linked to lower risk of breast cancer incidence, theoretically by lower sex hormone exposure.[9] This likely does not fully explain the lower risk in premenopausal women, given the low rates of amenorrhea in this population. Another hypothesis is that a reduction in progesterone, a promoter of breast cancer cell proliferation, in obese premenopausal women may be responsible for the protective effect of obesity on the risk of hormone receptor–sensitive breast cancer,[10] although the underlying mechanisms of risk in this population likely are more complicated. In contrast to hormone receptor–positive breast cancer, so far the data have not shown a strong association between obesity and the incidence of hormone receptor–negative breast cancer. This may be related to a different mechanism in the development of these cancers, or the lack of a clear signal may result from the study being underpowered or a smaller effect size in these subgroups. More basic science and correlative work is needed to help elucidate these mechanisms.

Obesity and Breast Cancer Mortality

Weight at Diagnosis

Obese women with breast cancer have worse overall survival and breast cancer–specific survival than nonobese women. Several recent meta-analyses have demonstrated an association between being overweight or obese at the

time of breast cancer diagnosis and increased risk of breast cancer–specific and all-cause mortality. A 2014 meta-analysis by Chan and colleagues that included 82 individual studies encompassing 213,075 women and 41,477 deaths found a 41% increased risk of total mortality and a 35% risk of breast cancer–specific mortality for obese women compared with normal-weight women.[11] For each 5-point increase in BMI, there was an 18% increase in the risk of breast cancer mortality (RR, 1.18; 95% CI, 1.12-1.25). Chan and colleagues also found an association between mortality and BMI at the time of diagnosis, less than 1 year after diagnosis, and greater than 1 year after diagnosis, demonstrating a persistent relationship between obesity and poor outcomes over time.

Studies have evaluated the relationship between menopausal status and the poor outcomes seen in obese women with early breast cancer. Chan and colleagues found that the relationship between BMI and breast cancer mortality was seen in both premenopausal and postmenopausal women, with obese premenopausal women having a 75% higher chance of overall mortality (RR, 1.75; 95% CI, 1.26-2.41) and obese postmenopausal women having a 34% higher chance of overall mortality (RR, 1.34; 95% CI, 1.18-1.53) than their normal-weight counterparts.[11] Other meta-analyses also have found that the relationship between obesity and excess mortality was numerically greater in premenopausal women than in postmenopausal women, although none of these studies found a statistically significant difference between the 2 groups.[12,13]

Studies also have evaluated whether the relationship between obesity at diagnosis and poor outcomes was seen across subtypes of breast cancer. Niraula and colleagues evaluated the relationship between obesity and breast cancer prognosis to determine whether there was an interaction based on the hormone receptor status of the tumor.[12] Obese women with hormone receptor–positive breast cancer had an HR for mortality of 1.31 (95% CI, 1.17-1.46) compared with normal-weight women with similar tumors, and obese women with hormone receptor–negative breast cancer had an HR of 1.18 (95% CI, 1.16-1.35) vs normal-weight women. Tests for interaction did not demonstrate a significant difference in the relationship between obesity and overall mortality by tumor type. Similarly, the breast cancer–specific survival was significantly worse in obese vs normal-weight women with both hormone receptor–positive (HR, 1.36; 95% CI, 1.20-1.54) and hormone receptor–negative (HR, 1.46; 95% CI, 0.98-2.19) cancers, but not statistically different from one another. It was therefore concluded that there was no differential effect of obesity on prognosis based on hormone receptor status.[12]

There is a strong association between obesity and the risk of breast cancer recurrence and mortality, regardless of menopausal status of the patient or hormone receptor sta-

tus of the cancer.[11-14] This is in contrast to the relationship between obesity and breast cancer risk, which seems to be elevated only in the setting of postmenopausal, hormone receptor–positive breast cancers. It is not entirely clear why obesity is associated with breast cancer risk only in a subgroup of patients, yet is related to the risk of cancer-related mortality across patient and tumor subtypes. It may be that the pathophysiologies of these 2 processes differ. As described earlier, a leading hypothesis for increased risk of developing breast cancer with obesity is increased sex hormones. Because endocrine therapies that block estradiol or prevent its production are used in the treatment of women diagnosed with hormone receptor–positive breast cancers, these treatments may impact hormonal signaling to the point where the more subtle effects of obesity on estradiol levels are not clinically relevant. A number of other pathways are under investigation that could explain the link between obesity and breast cancer prognosis. There is mounting evidence to suggest that insulin resistance,[15-17] metabolic syndrome,[18] inflammation,[19] and immune modulation[20] may be intermediaries between obesity and breast cancer mortality. It is likely that more than one mechanism is at work. Further biomarker work may provide additional insight into the mechanisms that underlie this clinical association.

Weight Change After Diagnosis

Few studies have evaluated the relationship between weight change after diagnosis and breast cancer prognosis. Playdon and colleagues conducted a meta-analysis of 12 studies, encompassing 23,832 women, to evaluate the relationship between weight gain after a breast cancer diagnosis and outcomes. They found that those who had a weight gain of at least 5% had an increased risk of all-cause mortality compared with those who maintained their weight (HR, 1.12; 95% CI, 1.03-1.22).[14] The investigators stratified participants by amount of weight gain and BMI at diagnosis and found that the risk appeared most pronounced in those with a weight gain of at least 10%.

Obesity and Other Adverse Outcomes in Women With Breast Cancer

Second Primary Malignancies

Obesity increases the risk that survivors of breast cancer will develop a second primary malignancy. A recent meta-analysis found that obesity was associated with a 37% increase in the RR of contralateral breast cancer (95% CI, 1.2-1.57), a 97% increase in the RR of endometrial cancer (95% CI, 1.43-2.70), and an 89% increase in the RR of colorectal cancer (95% CI, 1.28-2.79) in breast cancer survivors.[21] These finding likely are related to the fact that obesity is a risk factor for developing breast,

endometrial, and colorectal primary cancers in the general population. These findings have important implications for cancer screening in survivors of early breast cancer.

Lymphedema

Lymphedema of the arm is a known complication of breast cancer treatment, affecting between 8% and 21% of patients.[22] Greater extent of local therapy and obesity are the 2 most important and significant risk factors for developing this complication. At least 14 studies have found an association between obesity and lymphedema.[22] Prospective cohort studies have found the increase in the risk of lymphedema in obese vs normal-weight breast cancer patients to range from 1.16 to 2.93.[22] There are few data regarding rates of lymphedema in obese patients in the setting of sentinel lymph node procedures; it remains to be seen how recent trends to limit axillary surgery will impact rates of lymphedema in obese women with breast cancer.

Surgical Complications

A number of recent studies have demonstrated that obesity is associated with higher rates of surgical complications, including infection, seroma, and repeat operations, and is also linked to longer hospital stays and increased cost. In a claims-based study of 2403 obese and 5597 nonobese women undergoing breast surgery, the rate of overall complications, including infection, pain, delayed healing, implant removal, seroma, and hematoma, was 18.3% in obese women vs 2.2% in nonobese women (P<.001), with an OR of 11.8 in an analysis adjusted for diabetes (P<.001).[23] This higher risk of complications was seen across procedure types, including mastopexy, breast reconstruction, breast reduction, and breast augmentation. Another large study utilizing the National Surgical Quality Improvement Program data set, which included 15,937 women who underwent breast reconstruction, evaluated 30-day complication rates for those with a BMI of at least 40 vs those with a BMI of less than 30. The researchers demonstrated an increased risk of wound complications, return to the operating room, and surgical site infection (all P<.001) in obese women, as well as longer operative times (246 vs 216 min; P<.0001).[24] A smaller study of 551 patients undergoing breast reconstruction with implants showed similar findings, with overall complication rates of 9.9% in normal-weight women, 23.3% in overweight women, and 20.6% in obese women (P=.001). Additionally, BMI was found to be an independent and strong predictor of flap necrosis, infection, and seroma on adjusted analysis (P<.05).[25] A larger recent trial that included 55,903 patients with breast cancer confirms these findings; obese vs nonobese individuals had higher rates of overall complications (9.0% vs 5.9% for lumpectomy; P=.011 and 5.9% vs 4.8% for mastectomy; P=.005), leading to longer hospital stays and higher costs.[26]

Trials Evaluating Weight Loss in Women With Breast Cancer

Relatively few studies have looked at the feasibility or benefits of weight loss interventions in breast cancer patients. A systematic review by Reeves and colleagues describes 10 randomized controlled trials and 4 single-arm studies that were published through July of 2013.[27] These were all small studies, with sample sizes ranging from 24 to 102 participants for randomized controlled trials and 10 to 34 participants for single-arm studies. The interventions studied varied, but included in-person group counseling, in-person individualized counseling, and telephone counseling. The duration of the interventions ranged from 12 weeks to 1 year. Notably, 3 of these trials included only African American or Hispanic women. Weight loss of at least 5% was seen in 6 of the 10 randomized controlled trials and 2 of the 4 single-arm studies. Additionally, 9 of the 10 randomized controlled trials showed statistically significant weight loss with the intervention compared with the control.

The LISA Trial

In addition to the smaller trials included in the review by Reeves and colleagues, there have been a few larger-scale weight loss studies reported in the recent past in women with breast cancer, including the LISA trial. The LISA trial was a randomized trial of a telephone-based weight loss intervention in postmenopausal breast cancer survivors with a BMI of at least 24 who were undergoing therapy with letrozole.[28] The intervention was mail-based education plus a 2-year telephone-based program modeled on the Diabetes Prevention Program, and the control was mail-based education alone. The telephone intervention consisted of an intensive phase (5 weekly telephone sessions), a consolidation phase (biweekly telephone sessions for months 2-3 and monthly telephone sessions for months 4-6), and a maintenance phase (telephone sessions every 2 months for months 7-12 and every 3 months for months 13-24). The telephone calls lasted for 30 to 60 minutes; were conducted by lifestyle coaches; and were scripted, standardized, and semistructured. Key individualized goals were loss of 10% of body weight, a deficit of 500 to 1000 calories per day, an increase in physical activity, and behavioral change motivation. The study enrolled 338 women between 2007 and 2010, but was terminated early owing to loss of funding. Participants had an average age of 61 years and an average BMI of 31 and had T1, lymph node–negative breast cancer. The study demonstrated a weight loss of 4.3 kg vs 0.6 kg (5.3% vs 0.7%; P<.001) at 6 months and 3.1 kg vs 0.3 kg (3.6% vs 0.4%; P<.001) at 24 months in the intervention group compared with the control group. This study demonstrated that a telephone-based program that was based on the Diabetes Prevention Program was feasible in

cancer survivors and resulted in maintained weight loss over the 2-year intervention period.

The ENERGY Trial

The ENERGY trial (Exercise and Nutrition to Enhance Recovery and Good Health for You) was a 2-year intervention that enrolled 692 overweight or obese (BMI, 25-45) women from 4 US sites. Participants were randomly assigned to a weight loss intervention consisting of group in-person sessions, telephone-based counseling, and tailored newsletters, or to a less-intense control group consisting of 2 in-person sessions.[29] The intervention included a goal deficit of 500 to 1000 calories a day and 60 minutes a day of moderate activity. The women were, on average, 56 years old and 2 years from diagnosis, with an average BMI of 31. The majority of participants had stage I or II disease (83%) and were hormone receptor–positive (77%). At 12 months, the weight loss in the intervention group compared with the control was 6.0% vs 1.5% (P<.001). Weight loss was still significantly greater in the intervention group vs the control group at 24 months, at 3.7% vs 1.3%, respectively (P<.001). Secondary outcomes demonstrated higher levels of physical activity and lower blood pressure in intervention vs control patients during the 2-year follow-up period.

The LEAN Study

The LEAN study (Lifestyle, Exercise, and Nutrition) was a randomized controlled trial of 100 women who were randomly assigned to 1 of 3 arms: an in-person weight loss program, a telephone-based weight loss program, or usual care.[30] The in-person and telephone counseling programs consisted of 11 sessions over 6 months. Counseling sessions focused on reducing caloric intake, increasing physical activity, and supporting behavior change. Participants were, on average, 59.0 years old and 2.9 years from diagnosis, with an average BMI of 33.1. The majority of participants had stage I breast cancer (51%). Weight loss was 5.6 kg (–6.4%), 4.8 kg (–5.4%), and 1.7 kg (–2.0%) for women randomly assigned to in-person, telephone, and usual care groups, respectively (P=.001 comparing in-person to usual care; P=.009 comparing telephone to usual care, and P=.46 comparing in-person to telephone care). Those in the intervention groups also increased their minutes of moderate/vigorous exercise per week (114±130 in the in-person group, 96±154 in the telephone group, and 17±110 in the control group; P<.05). Additionally, C-reactive protein levels decreased by 30% in the intervention groups vs 1% in the control group (P=.05 for either intervention group vs the control group).

In aggregate, these studies suggest that lifestyle-based weight loss interventions lead to an average 5% to 6% weight loss at 6 to 12 months (Table 2).[28-30] This is consistent with weight loss seen in similar interventions in noncancer populations.[31] This amount of weight loss has been found to be beneficial for noncancer outcomes such as reducing the incidence of diabetes.[32]

Trials Evaluating the Effect of Weight Loss on Breast Cancer Outcomes

As discussed earlier, a growing body of data demonstrates that being overweight or obese at diagnosis, as well as weight gain after diagnosis, portend poorer cancer outcomes and higher mortality. It remains unknown whether weight loss in breast cancer survivors could improve cancer outcomes. This question is being addressed by 2 ongoing studies and 1 planned study, as described below.

The SUCCESS-C Trial

The SUCCESS-C trial (Docetaxel Based Anthracycline Free Adjuvant Treatment Evaluation, as Well as Life Style Intervention) is a randomized phase 3 trial with a 2 × 2 factorial design evaluating the impact of 2 different chemotherapy regimens, as well as the effect of a telephone-based lifestyle intervention on disease-free survival in 3547 women with early-stage, human epidermal growth factor receptor 2–negative breast cancer (NCT00847444).[33] Women with node-positive breast cancer or high-risk node-negative disease were randomly assigned to 3 cycles of epirubicin/5-fluorouracil/cyclophosphamide followed by 3 cycles of docetaxel vs 6 cycles of docetaxel/cyclophosphamide. Women with a BMI of 24 to 40 at enrollment were subsequently randomly assigned to a 2-year telephone-based lifestyle intervention vs a mailed general recommendation for healthy lifestyle care. The key goals were a loss of 5% to 10% of body weight; a deficit of 500 to 100 calories per day; and increased exercise, with a goal of 150 to 200 minutes per week of moderate aerobic activity. The trial's primary outcomes are the effect of the chemotherapy regimen and the lifestyle intervention on disease-free survival. Secondary outcomes are the effect of the lifestyle intervention on obesity-related biomarkers, genetic markers, circulating tumor cells, and the incidence of other obesity-related medical conditions (eg, diabetes, hypertension, and coronary artery disease). Accrual to this trial has completed and follow-up is ongoing.

The DIANA-5 Study

The DIANA-5 study (Diet and Androgens Study) is a randomized trial testing the impact of a Mediterranean lifestyle intervention on breast cancer recurrence in 1667 women with early-stage disease.[34] Eligibility criteria included breast cancer diagnosis within the past 5 years, and completion of chemotherapy and surgery. The study was open to women of any BMI, but women were only

Table 2. Recent Randomized Controlled Trials of Weight Loss Interventions in Breast Cancer Survivors

Study	N	Eligibility/Population	Intervention	Primary Outcome	Other Outcomes
LISA,[28] 2014	338 of 2150 planned, multicenter	Stage I-III, postmenopausal, on letrozole, BMI ≥24	2-year telephone-based intervention based on DPP (intensive, consolidation, and maintenance phases with focus on caloric deficit, increased physical activity, and behavior change motivation)	DFS: not different between groups, but underpowered given halted accrual	Weight loss: • 4.3 kg vs 0.6 kg at 6 months (5.3% vs 0.7%) • 3.1 kg vs 0.3 kg at 24 months (3.6% vs 0.4%)
ENERGY,[29] 2015	692 at 4 US sites (San Diego, CA; Denver, CO; St Louis, MO; Birmingham, AL)	Stages I-III (>1 cm), diagnosed <5 years prior, completed initial therapies (not including HRT), BMI 25-45	2-year group-based weekly × 4 months, bimonthly × 2 months, and monthly × 6 months, with e-mail/phone support, goals of 500-1000 calorie deficit, 60 min/day of mod physical activity, compared with control of 2 in-person diet counseling sessions and optional seminars	*Weight loss:* • 12 months: 6.0% vs 1.5% (*P*<.001) • 24 months: 3.7% vs 1.3% (*P*<.001)	Increased amount of mod/vig physical activity in the intervention group compared with the control group at 6 and 12 months. Both systolic and diastolic blood pressure was also lower in the intervention group vs the control group at all times (*P*<.05, except for 12-month diastolic)
LEAN,[30] 2016	100 at a single institution (Yale)	Stage I-III, BMI ≥25, average age 59 years, average BMI 33.1, 51% stage I	Randomized 1:1:1 intervention of in-person vs phone vs usual care based on DPP, including 11 sessions/6 months with goals of caloric deficit, increased physical activity, and behavior change motivation	*Weight loss at 6 months:* 6.4% (5.6 kg), 5.4% (4.8 kg), and 2.0% (1.7 kg), respectively (*P*=.001, *P*=.009), comparing interventions with usual care, and no difference between the intervention arms (*P*=.46)	*Physical activity change:* +114 vs +96 vs +17 min of mod/vig activity; +1847, +948, −330 steps/day *Serum markers:* 30% vs 1% decrease in CRP for intervention vs usual care

BMI, body mass index; CRP, C-reactive protein; DFS, disease-free survival; DPP, Diabetes Prevention Program; ENERGY, Exercise and Nutrition to Enhance Recovery and Good Health for You; HRT, hormone replacement therapy; LEAN, Lifestyle, Exercise, and Nutrition; LISA, Telephone-Based Weight Loss Intervention in Postmenopausal Women with Breast Cancer Receiving Letrozole; min, minutes; mod/vig, moderate or vigorous.

eligible for randomization to the intervention or comparison arm if they had metabolic syndrome, high testosterone, or high insulin levels, or if their tumors were hormone receptor–negative or involved lymph nodes. Women not meeting these criteria were placed in an observation-only arm (n=453). Eligible patients (n=1214) were randomly assigned to either a lifestyle intervention or a comparison group that received general health recommendations at randomization and a short refresher course 2 to 3 times each year. The lifestyle intervention goals included moderation of caloric intake, decreased intake of animal protein, and 210 minutes per week of exercise. This was accomplished through 4 cooking classes, 10 meetings with common meals, and monthly exercise sessions. The primary outcome of this trial will be the impact of the lifestyle intervention on breast cancer events, based on self-report with medical records verification. Secondary measures include hormonal and metabolic blood testing and anthropometric measures. Patient recruitment was completed in 2010. The average age of randomized participants is 51 years, and the average BMI is 26.

The BWEL Study
The BWEL study (Breast Cancer Weight Loss) is a phase 3 randomized trial sponsored by the National Cancer Institute and the Alliance for Clinical Trials in Oncology that will evaluate the impact of a telephone-based weight loss intervention on invasive disease–free survival in overweight and obese women with stage II or III breast cancer in the United States and Canada (NCT02750826).

The trial will enroll 3136 women. Key eligibility criteria include diagnosis of breast cancer within the past 12 months and BMI of at least 27. The intervention will be delivered over the course of 2 years, with individualized weight loss goals attained through caloric restriction and increased physical activity. The trial opened to enrollment in the summer of 2016.

Conclusions

Obesity is a growing problem worldwide. The relationship between obesity and cancer has been well-defined. Obese postmenopausal women are at increased risk of developing breast cancer, and obesity at the time of breast cancer diagnosis is a poor prognostic factor in both premenopausal and postmenopausal women. Obesity has additional ramifications for breast cancer patients, including an increased risk of second primary cancers and of morbidity resulting from breast cancer treatment. A number of trials have demonstrated the feasibility of implementing weight loss interventions in breast cancer populations. Ongoing studies will evaluate whether purposeful weight loss after breast cancer diagnosis could mitigate the poor outcomes seen in obese women, hopefully reducing the number of women who succumb to this disease each year.

Disclosures
The authors have no relevant disclosures to report.

References

1. SEER stat fact sheets: female breast cancer. National Cancer Institute. http://seer.cancer.gov/statfacts/html/breast.html. Accessed August 23, 2016.
2. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569-578.
3. Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. *Epidemiol Rev*. 2014;36:114-136.
4. Keum N, Greenwood DC, Lee DH, et al. Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. *J Natl Cancer Inst*. 2015;107(3):dju428.
5. Neuhouser ML, Aragaki AK, Prentice RL, et al. Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the Women's Health Initiative Randomized Clinical Trials. *JAMA Oncol*. 2015;1(5):611-621.
6. Bandera EV, Chandran U, Hong CC, et al. Obesity, body fat distribution, and risk of breast cancer subtypes in African American women participating in the AMBER Consortium. *Breast Cancer Res Treat*. 2015;150(3):655-666.
7. Key TJ, Appleby PN, Reeves GK, et al; Endogenous Hormones and Breast Cancer Collaborative Group. Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. *Br J Cancer*. 2011;105(5):709-722.
8. Key TJ, Appleby PN, Reeves GK, et al; Endogenous Hormones and Breast Cancer Collaborative Group. Steroid hormone measurements from different types of assays in relation to body mass index and breast cancer risk in postmenopausal women: reanalysis of eighteen prospective studies. *Steroids*. 2015;99(pt A):49-55.
9. Terry KL, Willett WC, Rich-Edwards JW, Michels KB. A prospective study of infertility due to ovulatory disorders, ovulation induction, and incidence of breast cancer. *Arch Intern Med*. 2006;166(22):2484-2489.
10. Dowsett M, Folkerd E. Reduced progesterone levels explain the reduced risk of breast cancer in obese premenopausal women: a new hypothesis. *Breast Cancer Res Treat*. 2015;149(1):1-4.
11. Chan DS, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol*. 2014;25(10):1901-1914.
12. Niraula S, Ocana A, Ennis M, Goodwin PJ. Body size and breast cancer prognosis in relation to hormone receptor or menopausal status: a meta-analysis. *Breast Cancer Res Treat*. 2012;134(2):769-781.
13. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. *Breast Cancer Res Treat*. 2010;123(3):627-635.
14. Playdon MC, Bracken MB, Sanft TB, Ligibel JA, Harrigan M, Irwin ML. Weight gain after breast cancer diagnosis and all-cause mortality: systematic review and meta-analysis. *J Natl Cancer Inst*. 2015;107(12):djv275.
15. Irwin ML, Duggan C, Wang CY, et al. Fasting C-peptide levels and death resulting from all causes and breast cancer: the health, eating, activity, and lifestyle study. *J Clin Oncol*. 2011;29(1):47-53.
16. Goodwin PJ, Ennis M, Pritchard KI, et al. Insulin-like growth factor binding proteins 1 and 3 and breast cancer outcomes. *Breast Cancer Res Treat*. 2002;74(1):65-76.
17. Goodwin PJ, Ennis M, Pritchard KI, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol*. 2002;20(1):42-51.
18. Berrino F, Villarini A, Traina A, et al. Metabolic syndrome and breast cancer prognosis. *Breast Cancer Res Treat*. 2014;147(1):159-165.
19. Pierce BL, Ballard-Barbash R, Bernstein L, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *J Clin Oncol*. 2009;27(21):3437-3444.
20. Kitahara CM, Trabert B, Katki HA, et al. Body mass index, physical activity, and serum markers of inflammation, immunity, and insulin resistance. *Cancer Epidemiol Biomarkers Prev*. 2014;23(12):2840-2849.
21. Druesne-Pecollo N, Touvier M, Barrandon E, et al. Excess body weight and second primary cancer risk after breast cancer: a systematic review and meta-analysis of prospective studies. *Breast Cancer Res Treat*. 2012;135(3):647-654.
22. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol*. 2013;14(6):500-515.
23. Chen CL, Shore AD, Johns R, Clark JM, Manahan M, Makary MA. The impact of obesity on breast surgery complications. *Plast Reconstr Surg*. 2011;128(5):395e-402e.
24. Fischer JP, Cleveland EC, Nelson JA, et al. Breast reconstruction in the morbidly obese patient: assessment of 30-day complications using the 2005 to 2010 National Surgical Quality Improvement Program data sets. *Plast Reconstr Surg*. 2013;132(4):750-761.
25. Nguyen KT, Hanwright PJ, Smetona JT, Hirsch EM, Seth AK, Kim JY. Body mass index as a continuous predictor of outcomes after expander-implant breast reconstruction. *Ann Plast Surg*. 2014;73(1):19-24.
26. Sun SX, Greenleaf EK, Hollenbeak CS, Leung AM. Attributable cost of obesity in breast surgery: a matched cohort analysis. *Am J Surg*. 2015;210(4):668-677. doi:10.1016/j.amjsurg.2015.06.003.
27. Reeves MM, Terranova CO, Eakin EG, Demark-Wahnefried W. Weight loss intervention trials in women with breast cancer: a systematic review. *Obes Rev*. 2014;15(9):749-768.
28. Goodwin PJ, Segal RJ, Vallis M, et al. Randomized trial of a telephone-based weight loss intervention in postmenopausal women with breast cancer receiving letrozole: the LISA trial. *J Clin Oncol*. 2014;32(21):2231-2239.
29. Rock CL, Flatt SW, Byers TE, et al. Results of the Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) trial: a behavioral weight loss intervention in overweight or obese breast cancer survivors. *J Clin Oncol*. 2015;33(28):3169-3176.
30. Harrigan M, Cartmel B, Loftfield E, et al. Randomized trial comparing telephone versus in-person weight loss counseling on body composition and circulating biomarkers in women treated for breast cancer: the Lifestyle, Exercise, and Nutrition (LEAN) study. *J Clin Oncol*. 2016;34(7):669-676.
31. Leblanc ES, O'Connor E, Whitlock EP, Patnode CD, Kapka T. Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011;155(7):434-447.
32. Knowler WC, Fowler SE, Hamman RF, et al; Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374(9702):1677-1686.
33. Rack B, Andergassen U, Neugebauer J, et al. The German SUCCESS C Study - the first European lifestyle study on breast cancer. *Breast Care (Basel)*. 2010;5(6):395-400.
34. Villarini A, Pasanisi P, Traina A, et al. Lifestyle and breast cancer recurrences: the DIANA-5 trial. *Tumori*. 2012;98(1):1-18.