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The association between adiposity and breast cancer recurrence and survival: A review of the recent literature

Maria Azrad, PhD, RD¹ and Wendy Demark-Wahnefried, PhD, RD^{1,2}

¹Department of Nutrition Sciences, University of Alabama at Birmingham (UAB), 1824 6th Avenue, 310B Wallace Tumor Institute, Birmingham, AL 35294

²UAB Comprehensive Cancer Center, University of Alabama at Birmingham, 1824 6th Avenue, 310D Wallace Tumor Institute, Birmingham, AL 35294

Abstract

Breast Cancer (BC) is the most common and second deadliest malignancy among American women. Many factors contribute to BC prognosis but a key modifiable lifestyle factor is body weight. In this review, we update the reader on the association between adiposity and poor BC outcomes. We summarize the findings from studies that show obesity to be a risk factor for BC recurrence and reduced survival, including research that shows that treatment with aromatase inhibitors in hormone-receptor positive BC survivors who are obese may not be as effective as in normal weight women. In addition, we summarize the findings from studies that show that obesity-induced changes in glucose metabolism, type-2 diabetes and metabolic syndrome contribute to negative outcomes in BC survivors. Given the evidence, there is a critical need to determine whether weight loss can improve outcomes in BC survivors.

Keywords

breast neoplasms; recurrence; survival; mortality; aromatase; aromatase inhibitor; adiposity; obesity; overweight; body fat; body mass index; body weight; insulin; estrogen-receptor positive; hormone-receptor positive; estrogen; glucose; glucose metabolism; c-peptide; HOMA; type 2 diabetes; metabolic syndrome; hormones

Introduction

Combined improvements in public awareness and screening have led to earlier detection and diagnosis of breast cancer (BC). As a result, the incidence of invasive BC has declined.[1] However, BC remains the most prevalent non-cutaneous malignancy in US women. Over 200,000 new cases of BC will be diagnosed in 2013.[1] Advances in treatment, particularly targeted-therapies aimed at molecular subtypes, have improved BC outcomes. Currently, there are 2.9 million female BC survivors in the US. While most women will remain disease free, many will experience disease recurrence and some will die from BC. BC is the second leading cause of cancer death, with greater than 40,000 women expected to die this year.[1]

Corresponding author: Dr. Maria Azrad (maria123@uab.edu).

Compliance with Ethics Guidelines

Conflict of Interest

Maria Azrad and Wendy Demark-Wahnefried declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Several studies have identified risk factors for aggressive BC and poor prognosis. Advanced stage and younger age at diagnosis, African-American ethnicity, positive lymph nodes, and triple negative tumors are key factors associated with poor BC outcomes. While these factors are not modifiable, lifestyle factors which also influence BC outcomes have been identified from epidemiological studies. Body weight, which is partly determined by genetic factors but also greatly influenced by caloric intake and expenditure through physical activity, is a modifiable lifestyle factor. Higher body mass index [BMI: body weight(kg)/height(m²)], a measure of adiposity, has been shown to be associated with poor BC outcomes. Protani et al. conducted a systemic review and meta-analysis that included 43 studies published between 1988–2009 and showed that women who are obese at the time of diagnosis (BMI>30), were 33% more likely to die from BC compared to non-obese women (1.33; 95%CI 1.19–1.50).[2] From a public health perspective, this is particularly concerning given that the majority of women diagnosed with invasive BC, women between 45–74 years old, are obese.[3,4]

The physiological changes associated with obesity have been well characterized, but how these factors mediate cancer outcomes are poorly understood. Higher circulating levels of insulin and glucose, onset of type 2 diabetes, and metabolic syndrome are all hallmarks of obesity.[5] There is a growing body of literature linking diabetes and metabolic syndrome to cancer.[6, 7] Recent studies have begun to elucidate how these diseases which center on abnormal glucose metabolism contribute to negative prognosis for BC. Excess fat tissue in postmenopausal women results in higher blood concentrations of estrogen through the conversion of androgens to estrogen by the aromatase enzyme in peripheral fat tissues.[8] This is particularly important in women diagnosed with hormone-receptor positive tumors. While endocrine-treatment with aromatase inhibitors (AIs) has markedly improved BC outcomes, there is accumulating evidence that obese women may not fully benefit from these agents.[9]

The purpose of this review is to update the reader on the most current literature pertaining to the association between obesity and BC recurrence, BC-specific mortality and overall mortality. We summarized the findings from prospective and retrospective studies, as well as secondary analyses from clinical trials that were published in English since 2010. Given the need to understand the potential biological mechanisms driving this relationship, we also included findings from studies that reported associations between diabetes, metabolic syndrome, and BC prognosis.

Obesity and risk for BC recurrence, BC-specific mortality and overall mortality

We identified 11 studies that were published since the 2010 paper of Protani et al. that investigated the relationship between obesity and BC outcomes.[2] Four studies were retrospective investigations that utilized data from medical record abstraction, an additional four studies were population-based epidemiological investigations, and three were secondary analyses from clinical trials that tested the efficacy of chemotherapy and endocrine treatments.

Retrospective studies

Jiralerspong et al. conducted a large a single-site study of 6,342 Stage I-III patients of whom 77% were estrogen-receptor (ER)-positive and 21% were HER2-positive.[10] After 5-year follow-up, overweight versus normal weight women had significantly inferior recurrence-free survival (Hazards Ratio [HR] 1.18; 95% Confidence Interval [CI] 1.02–1.36) overall survival (HR1.20; 95%CI 1.00–1.42) and BC specific survival (HR 1.21; 95%CI 0.98–1.48).

Additionally, obese women versus normal weight had worse recurrence-free survival (HR 1.13; 95% CI 0.98–1.31), overall survival (HR 1.24; 95% CI 1.04–1.48) and BC specific survival (HR 1.23; 95% CI 1.00–1.52). Obesity and poor BC outcomes were significantly related to women with ER-positive tumors, but not ER-negative or HER2-positive tumors. [10]

Kamineni and colleagues used data from women enrolled in the Group Health Cooperative system to investigate the association between BMI at the time of mammography screening and risk for recurrence and mortality (n=485 women with early-stage BC). [11] In multivariate analyses that adjusted for age, stage, and tamoxifen-use, obese women had a non-significant risk for BC mortality (HR 2.41; 95% CI 1.00–5.81) and a significantly higher risk of recurrence (HR 2.43; 95% CI 1.34–4.41). Notably, this study observed that obese women had higher tumor proliferation rates (Ki67) relative to normal weight women. [11]

Conversely, Ademuyiwa and colleagues conducted a study of 481 women with stage I-III triple negative BC. [12] No association between BMI and recurrence-free survival or overall survival was observed. [12] Dawoo et al. conducted a comparable single-institution, retrospective study that included 2311 women with triple-negative tumors and stage I-III BC. [13] Similar to the findings from Ademuyiwa et al., no association between obesity and BC outcomes were observed. It should be noted that both of these studies were limited by their brief follow-up time of ~3-years.

Secondary analyses from clinical trials

The Breast International Group (BIG) 02–08 was a clinical trial that showed that sequential administration of docetaxel increases disease-free survival versus anthracycline-based chemotherapy in node-positive BC patients. [14] In secondary analyses, de Azambuja et al. explored whether obesity influenced clinical outcomes in 547 obese versus 2,340 non-obese BC survivors. [15] After 5-year follow-up, obese women had significantly worse overall survival (HR 1.34; 95% CI 1.06–1.69) and disease-free survival (HR 1.2; 95% CI 1.01–1.44). Further analyses showed that obese women with ER-positive and PR-negative tumors had significantly lower overall survival (HR 1.91; 95% CI 1.17–3.12) and disease-free survival (HR 1.63; 95% CI 1.16–2.38). Of note, one limitation of this study was the absence of HER2-status. [15]

Using data collected from three clinical trials that tested chemotherapy and endocrine therapy regimens, Sparano et al. performed secondary analyses comparing the outcomes of obese versus non-obese patients at the time of diagnosis of stage I-III BC. [16] Analyses from E1199, a clinical trial for women diagnosed with ER-positive HER2 negative/unknown disease, showed inferior disease-free survival (HR 1.24; 95% CI, 1.06–1.46), overall survival (HR 1.37; 95% CI 1.13–1.67) and BC-specific survival (HR 1.40; 95% CI 1.11–1.76) for obese versus non-obese women treated with chemotherapy and endocrine therapy. In analyses of E5188, that included only premenopausal women with ER-positive tumors (HER2 status unknown) and node-positive disease, similar results were found with obese women having poorer disease-free survival (HR 1.41; 95% CI, 1.19–1.67), overall survival (HR 1.51; 95% CI 1.24–1.83) and BC-specific survival (HR 1.54; 95% CI 1.26–1.88). Analyses for the E3189 trial, which included women diagnosed with ER-PR-negative disease and HER2-unknown, did not show an association between obesity and BC outcomes. [16]

Crozier et al. used data from a previous clinical trial, which included 3,017 women with HER2-positive tumors treated with chemotherapy with or without sequential or concurrent trastuzumab, to investigate the association between obesity and disease-free survival. [17] After 5-year follow-up disease free survival was worse in overweight versus normal weight

women (HR 1.30; 95%CI 1.06–1.61) and obese versus normal weight women (HR 1.31 95%CI 1.07–1.59). The 5-year disease-free survival rates were 82.5%, 78.6%, and 78.5% for normal weight, overweight, and obese women, respectively.[17]

Population-based studies

Ewertz et al. analyzed the association between BMI and BC outcomes in the Danish BC Cooperative Group, which included 53,816 women with 10-year follow-up.[18] While no differences in risk for local recurrence were observed across BMI categories (BMI<25, BMI=25–29, BMI>30 and unknown), overweight women had 42% (HR 1.42; 95%CI 1.17–1.73) and obese women had 46% (HR 1.46; 95%CI: 1.11–1.92) higher risk for distant metastases after 5–10 year follow-up when compared to normal weight women. Overweight women also had higher risk of dying from BC compared to normal weight women (HR 1.26 95%CI 1.09–1.46).

The After BC Pooling Project (ABCP), which included four prospective studies [the Shanghai BC Survival Study (SBCSS), the Life after Cancer Epidemiology (LACE) Study, the Nurses' Health Study (NHS), and the Women's Healthy Eating and Living ((WHEL Study)], investigated recurrence, and BC-specific, non-BC, and total mortality in 14,948 women diagnosed with stage I-III BC.[19] After nearly 8-year follow-up, there was no association between BMI and increased risk of recurrence or BC-specific mortality. However obese women had increased risk of non-BC mortality and total mortality compared to normal-weight women (HR 1.33; 95%CI 1.10–1.62 and HR 1.17; 95%CI 1.04–1.32). In addition, women with BMI=35–39.9 had increased risk of non-BC mortality (HR 1.40; 95%CI 1.02–1.92); and women with BMI>40 had increased risk for BC mortality (HR 1.40; 95%CI: 1.00–1.96), non-BC mortality (HR 3.01; 95% CI: 2.09–4.33) and total mortality (HR 1.81; 95%CI 1.41– 2.32) compared to normal weight women.[19]

Chen et al. investigated associations between BMI (1-year before, at diagnosis, and 6 and 18 months post-diagnosis) with total mortality and BC-specific mortality in a population-based study in China that included women with stage 0-IV BC.[20] After nearly 4-years follow-up, women who were obese 1-year prior to diagnosis had higher total mortality (HR 1.58; 95%CI 1.13–2.22) compared to normal weight women. Women obese at diagnosis had higher rates of BC-specific mortality (HR 1.44; 95%CI 1.02–2.03) and total mortality (HR 1.55; 95%CI 1.10–2.17). Similar risk for BC-specific mortality was seen for women who were obese 6-months post-diagnosis compared to normal weight women. Gains in weight from 1-year prior to diagnosis to 18-months post-diagnosis of 1–5 kg or 5 kg were associated with increased risk for BC-specific mortality (HR 1.97; 95%CI 1.30–2.97, HR 1.90; 95%CI 1.23–2.93, respectively) and total mortality (HR 1.89; 95%CI 1.27–2.82, HR 1.71 95%CI 1.12–2.60, respectively). Women who gained 5 kg between diagnosis and 18-months post-diagnosis had increased risk for total mortality (HR 1.54; 95% CI 1.03–2.29).

In a cohort of 3,842 of post-menopausal women diagnosed with stage I-II BC from the Multiethnic Cohort (MEC) and followed for 6-years, women who were obese at diagnosis were at increased risk of all-cause mortality (HR 1.54; 95%CI 1.23–1.91) and BC-specific mortality (HR 1.45; 95%CI 1.05–2.00) compared to normal weight women.[21] Notably, no ethnic/racial differences were observed regarding the association between obesity and BC outcomes in this cohort of Caucasian, African-American, Hispanic, Native-Hawaiian and Japanese-American women.

From the results of the above studies several conclusions can be made. First, obesity, particularly morbid obesity, and in some cases overweight, contribute to negative clinical outcomes in BC patients. Second, the association between obesity and BC is apparent in several ethnic populations. Third, the association between obesity and poor BC outcomes

appears to be strongest in women with ER-positive tumors regardless of menopausal status. Finally, obesity may negatively affect BC outcomes in women with HER2-positive but more studies are needed; whereas there is no evidence to suggest that obesity is associated with outcomes in women with triple negative disease, though periods of extended follow-up may be needed to definitively make these conclusions.

Obesity may alter the efficacy of treatment for hormone-receptor positive tumors

The use of aromatase inhibitors (AI) is standard therapy in postmenopausal women diagnosed with hormone-receptor positive BC.[22] AIs block the aromatase enzyme from converting androgens to estrogen hence hindering the growth of new, residual or dormant BC cells. The aromatase enzyme is expressed in peripheral fat tissue and thus postmenopausal women with higher BMI tend to have higher levels estrogen. Whether, higher BMI attenuates the effectiveness of AIs and negatively effects BC outcomes is a concern. Below, we summarize recent findings from four clinical trials that assessed associations between BMI and BC outcomes in patients receiving AIs.

The Arimidex, Tamoxifen Alone or in Combination (ATAC) trial, was a randomized double-blind study that showed significant improvements in BC outcomes in women with early-stage hormone-receptor positive BC taking arimedex versus tamoxifen.[23] In analyses that compared the effectiveness of arimedex and tamoxifen in regard to overall recurrence, tamoxifen was found equally effective across all BMI levels, suggesting that obesity did not alter the effectiveness of tamoxifen.[24] However, after 8-year follow-up, 878 of 4,939 women on arimedex recurred, and those who were obese (BMI>35) at baseline were significantly more likely to have disease recurrence and distant recurrence compared to women with BMI<23 (HR 1.39; 95%CI 1.06–1.82 and HR 1.46; 95%CI 1.07–1.61, respectively). The authors concluded that obese women have a significantly higher recurrence rate, both overall and at distant sites and that aromatase enzyme suppression by arimedex may not be fully effective in obese postmenopausal women.

Similarly, the Austrian Breast and Colorectal Cancer Study Group trial 6 (ABCSG-6) investigated the efficacy of tamoxifen alone or concurrently with aminoglutethimide and found no between-arm differences in disease-free survival after 5-year follow-up.[25] A secondary analysis on 1509 patients found that overweight women had poorer distant-recurrence-free survival compared to normal weight women (HR 1.54; 95%CI 1.00–2.35) and obese women had poorer disease-free survival (HR 1.45; 95%CI 1.03–2.02), distant recurrence-free survival (HR 1.79; 95%CI 1.11–2.87 and overall survival (HR 1.82; 95%CI 1.12–2.91) compared to normal weight women.[26] Obese women in the tamoxifen + AI group also had worse disease-free survival (HR 1.78; 95%CI 1.12–2.83), distant recurrence-free survival (HR 2.43; 95%CI 1.25–4.70) and overall survival (HR 2.28; 95%CI 1.16–4.51) compared to normal weight women receiving tamoxifen + AI. No differences across BMI were detected in the tamoxifen only group [26]

Following completion of the ABCSG-6 trial, the ABCSG-6a trial began and event-free women were re-randomized to either 3-years of anastrozole or no treatment.[27] After 5-year follow-up, anastrozole was proven effective in reducing the risk of recurrence. Secondary analyses on 634 women found no differences in risk for distant metastasis, disease-free survival and overall survival between normal weight and overweight or obese women.[28] Significantly better outcomes, however were seen among normal weight women receiving anastrozole, whereas no protection was observed among women who were overweight or obese.

In the ABCSG-12 trial, premenopausal women with stage IB, IC or II, hormone-receptor positive BC were randomly assigned to 1-of-4 groups: goserelin (luteinizing hormone releasing hormone agonist) + tamoxifen or goserelin + anastrozole with or without zoledronic acid for 3-years.[29] After nearly 4-years of follow-up, analyses showed that there was no significant difference in disease-free survival between the tamoxifen and anastrozole arms that received goserelin. However, the treatment arms that received either agent plus zoledronic acid had significantly better outcomes compared to arms that did not receive zoledronic acid. Secondary analyses performed on the 1,684 women receiving endocrine therapy showed no differences in disease-free or overall survival by weight status over 5-years of follow-up[30]. However, in the anastrozole arm significant differences between normal weight and overweight/obese women were observed for risk of recurrence (HR 1.53; 95% CI 1.01–2.31) and overall survival (HR 1.93; 95% CI 1.04–3.58). In additional analyses, no differences in BC outcomes were observed when normal weight women in the tamoxifen arm were compared to the anastrozole arm. In contrast, overweight + obese women in the anastrozole arm tended to have significantly higher risk for reduced disease free survival (HR 1.47; 95% CI 0.90–2.40) and overall survival (HR 3.23; 95% CI 1.39–7.53) compare to overweight + obese women taking tamoxifen.

Taken as a whole, the results from clinical trials confirm that adiposity is a key risk factor for recurrence in both premenopausal and postmenopausal women with hormone-receptor positive BC. Importantly, these studies suggest that AIs may not be fully effective in women who are obese. It should be noted that these clinical trials did not measure endogenous estrogen levels before or after AI initiation and therefore it is difficult to understand whether estrogen alone or synergistically with other obesity-related factors are driving poor outcomes in this patient population.[31]

Obesity-related mechanisms associated with poor BC outcomes

Glucose metabolism, type 2 diabetes and metabolic syndrome

The changes in the hormonal milieu brought on by obesity provide a host-environment that likely favors cancer cell growth. However, these factors generally do not occur as single events but rather in complex synergy. In addition to higher estrogen levels seen in obese postmenopausal women, another common endocrine factor seen with higher adiposity is the onset of higher glucose and insulin concentrations, type 2 diabetes, and metabolic syndrome, which includes abnormal glucose metabolism as well as hypertension and dyslipidemia. Because obesity and metabolic changes are common in BC survivors, several recent studies have investigated whether these factors influence BC prognosis. Below, we summarize the findings from seven recent investigations.

The MEC study observed that after 6-year follow-up women with diabetes had significantly higher all-cause mortality (HR 2.05; 95% CI 1.70–2.48) and BC-specific mortality (HR 1.46; 95% CI 1.06–2.01) independent of obesity.[21] Erickson et al. investigated the association between diabetes and BC outcomes in the Women's Healthy Eating and Living WHEL) study, a multi-site randomized trial that promoted improved diet quality without weight loss. After 7-year follow-up, multivariate analyses adjusting for stage, grade, age, ethnicity, education, physical activity, and physical health showed that BC survivors with hemoglobin A1C ≥ 7 had significantly lower overall survival compared to women with levels <6.5 . [32] Because hemoglobin A1C >6.5 is indicative of diabetes, these results suggest that BC survivors with diabetes are more likely to die than those with normal glucose metabolism. Surprisingly, this study also showed that most women with elevated hemoglobin A1C did not report having diabetes suggesting that they were unaware of their abnormal glucose metabolism.[32]

In a study of 530 BC survivors, Goodwin et al. investigated the prognostic associations between markers of glucose metabolism and risk for distant recurrence.[33] Insulin, glucose, homeostatic model assessment (HOMA - a proxy for insulin-sensitivity) and c-peptide were significantly associated with increased risk for distant recurrence within 0–5 years of diagnosis in adjusted multivariate analyses.

The association between HOMA and BC outcomes also was assessed in the Health, Eating, Activity, and Lifestyle (HEAL) observational study. In analyses that included 527 women with stage I-IIIa BC, Duggan et al. observed higher HOMA scores were significantly associated with BC mortality in women with stage III disease (HR 1.20 95%CI 1.09–1.33); ER-positive tumors (HR 1.19; 95%CI 1.09–1.31); and of African-American descent (HR 1.19; 95%CI 1.08–1.32).[34] Also in the HEAL study, Irwin et al. found that C-peptide, a sensitive biomarker of systemic insulin exposure, was independently associated with increased risk of BC death.[35]

Minicozzi et al. utilized the Italian Association of Cancer Registries database to identify BC patients enrolled in the EURO CARE study, a collaborative research project on cancer survival in Europe. After 4-year follow-up, no overall association between diabetes and BC outcomes was observed. However, women with ER- and PR-positive tumors who had higher fasting glucose were significantly more likely to die from BC (highest versus middle tertile, HR 5.49; 95%CI 1.56–19.31). There was no association between fasting glucose or BMI with BC death in women with ER- and PR- tumors.[36]

Bjorge and colleagues evaluated the association between metabolic syndrome and death from BC in the METabolic syndrome and CANcer (Me-Can) project. After 11-year follow-up, 633 out of 287,320 women died from BC. Multivariate analyses suggest that metabolic syndrome was positively associated with risk for BC mortality in women 60 years (RR 1.23; 95% CI 1.04–1.45) but not in younger women. Higher blood glucose concentrations tended to be associated with BC death, but did not reach statistical significance.[37]

Collectively, these studies show that abnormal glucose metabolism, type 2 diabetes, and metabolic syndrome in BC patients confers negative outcomes. This is concerning given that the obesity epidemic has brought on a surge in the incidence of these metabolic disorders. Equally concerning is the observation that many BC survivors may be unaware that they have abnormal glucose metabolism. Whether improvements in glucose metabolism can improve outcomes in BC survivors remains unclear, but could be a means of cancer control in this patient population.

Conclusions

The studies included in this review support extant findings that obesity at the time of BC diagnosis is a poor prognostic factor. Current findings suggest that this relationship is similar across racial/ethnic groups. Although at present obesity does not appear to influence outcomes in women with triple-negative disease, it may influence outcomes in women with HER2 positive tumors and likely plays a key role in outcomes in women with hormone-receptor positive BC. One key factor in this relationship is higher estrogen in obese women with hormone-receptor positive tumors. Most concerning is evidence that obese women do not receive the same protection from AIs as normal weight women. Other key factors in the relationship between obesity and poor BC outcomes are abnormal glucose metabolism and the presence of metabolic syndrome and type 2 diabetes, which appear to also contribute to negative outcomes.

While the complex relationship between obesity and poor BC prognosis has received much attention, questions remain in the quest to improve BC outcomes. What are the biological

mechanism(s) driving this relationship? Can intentional weight loss lower the risk for recurrence and improve survival, and if so, how much weight loss is needed to achieve better outcomes? To answer these questions, long-term follow-up studies are critically needed so that standard clinical care could potentially be adapted to improve outcomes in obese women with BC –the largest and fastest growing population of cancer survivors in the US.

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