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REVIEW

The Role of Obesity and Inflammation in Breast Cancer Recurrence

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Abstract

Purpose of review The purpose of this study is to summarize the latest findings regarding the impact of obesity and inflammation on breast cancer recurrence risk.

Recent Findings Obesity is a risk factor for breast cancer recurrence and cancer-specific mortality. Biologic mechanisms that drive this association vary by tumor subtype and include a dysfunctional tumor microenvironment and systemic inflammation. We discuss the impact of obesity on systemic therapy resistance and review current evidence supporting pharmacological, surgical, and lifestyle modifications for addressing obesity in the context of improving breast cancer survivorship.

Summary Obesity is associated with poorer survival in breast cancer. Risk stratification by tumor and host-specific characteristics can help identify adjunctive interventions to improve breast cancer outcomes in patients with obesity.

Keywords Breast cancer · Inflammation · Obesity · Recurrence · Survivorship

Introduction

Breast cancer (BC) is the most common non-cutaneous cancer type in women and comprises 15% of all new cancer cases with an estimated 290,000 new cases diagnosed in the United States in 2023 [1]. Obesity is an established risk factor for the incidence and recurrence of several cancers, though the effects of obesity vary by tumor subtype and other metabolic factors. Lifestyle and pharmacologic interventions targeting the tumor-promoting effects of obesity may be leveraged to reduce resistance and/or improve efficacy of curative-intent adjuvant therapies. In this article, we briefly review mechanisms linking obesity to BC recurrence and focus on updates in the understanding of obesity as a mediator of treatment response and recent advances in anti-obesity interventions that could impact cancer outcomes.

Overview of Mechanisms Linking Obesity to Breast Cancer Recurrence

Obesity has reached pandemic proportions with a prevalence of approximately 14% worldwide, affecting over 1 billion people. In the United States, approximately 50% of women are obese and a further 28% are overweight [2•, 3]. Overweight and obesity are classically defined by a body mass index (BMI) of 25.0 to < 30 kg/m^2 and ≥30.0 kg/m^2, respectively, while severe obesity refers to a BMI ≥40.0 kg/m^2 [3]. Abdominal obesity by waist circumference (defined as > 88 cm in women by the World Health Organization [4]) is one of the criteria for the diagnosis of metabolic syndrome (MetS), which also includes hypertension, hyperglycemia, and hyperlipidemia. Large prospective studies and metanalyses have shown that obesity is associated with an increased risk of all-cause mortality [5]. Obesity is associated with an increased risk of incident BC, BC recurrence, and BC-specific mortality [6•].

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In the post BC diagnosis setting, obesity is associated with increased risk of recurrence, worse cancer-specific survival, and worse overall survival (OS), which may be driven by the strong association in hormone receptor-positive BC in both premenopausal and postmenopausal patients [7, 8]. Obese women with hormone receptor-positive BC have increased BC mortality (hazard ratio [HR] 1.78; 95% confidence interval [CI] 1.28–2.48) compared to human epidermal growth factor receptor 2 positive (HER2 +) BC (HR 1.09; 95% CI 0.14–8.84) and triple negative BC (HR 1.18; 95% CI 0.54–2.57) [8]. However, obesity in premenopausal women has not been associated with increased BC mortality (HR = 2.1; 95% CI 0.8–5.1) compared to postmenopausal obese women (HR = 1.4; 95% CI 1.0–2.1) [8].

Additionally, obese BC survivors have an increased risk of developing metastatic recurrence at multiple sites [9•]. However, there are mixed findings on the impact of obesity on metastatic BC survival, with conflicting data depending on subtype and lines of therapy received [10, 11•, 12]. One study found obesity to be an independent predictor of poorer OS in metastatic BC (HR = 7.1; 95% CI 4.4–8.7) [10], while others noted no impact of obesity on OS in metastatic BC [11•, 12].

Adipose tissue dysfunction is a central mediator of obesity-driven cancer growth. White adipose tissue is an active endocrine organ that is responsible for energy homeostasis, and excess adiposity promotes chronic inflammation which establishes a pro-neoplastic tumor microenvironment (TME) [13]. The TME plays an important role in the development, growth, and progression of cancer. Adipose inflammation disrupts adipocytokine balance to favor the production of leptin and cytokines such as tumor necrosis factor-α (TNF-α) which are known to promote tumor growth via angiogenesis, enhanced cell migratory capacity, and genomic instability [14•]. Inflammasome activation drives interleukin-1β signaling in the tumor which stimulates vascular endothelial growth factor A expression, ultimately promoting tumor angiogenesis. Increased myofibroblast content leads to stiffened extracellular matrices and enhanced cancer cell growth, while increased epithelial to mesenchymal transition and promotion of neutrophil expansion enhances the ability for metastatic spread [15]. The microbiome also plays a role in controlling the immune system and mediating inflammation [16]. The microbiota of breast tissue in BC patients have been shown to contain increased cohorts of bacteria with known procarcinogenic effects compared to healthy controls, although further research is required to ascertain whether the differences in the bacterial profiles are truly pathogenic [17]. Molecular features of BC have also been found to differ according to BMI, with differentially prevalent genomic driver alterations in overweight/obese patients compared to lean patients (e.g., higher prevalence of PIK3CA in obese patients compared to lean patients 22.2% vs 9.8%, $p = 0.011$) [18]. Genomic and transcriptomic data indicate that obesity promotes an inflammatory-like phenotype in BC, whereby chronic low-grade inflammation contributes to disease pathogenesis [18, 19••].

Other key mechanisms that drive BC recurrence include increases in bioavailable estrogens and insulin resistance [20]. More active aromatization of androgens in peripheral adipose tissue increases local estrogen production, and decreases in sex hormone-binding globulin further increase circulating bioavailable estrogens [21]. Adipose inflammation, specifically the production of cytokines interleukin-6 and TNF-α, also increases aromatase production via autocrine and paracrine signaling [22]. Cancer cells often overexpress the insulin receptor which promotes growth and survival [23]. Insulin, insulin-like growth factor-1 (IGF-1), and several IGF-binding proteins act as growth factors, thereby promoting cancer cell proliferation [24•]. Binding of insulin to the insulin receptor causes tissue-specific metabolic effects, which include increased cellular glucose uptake, cell proliferation, and inhibition of apoptosis [25]. Additionally, hyperinsulinemia affects sex hormone levels which can directly stimulate hormonally driven cancers like hormone receptor-positive BC [26]. Insulin resistance is associated with significant increases in BC-specific mortality, with women in the highest versus those in the lowest insulin resistance quartile having a greater risk of death after BC (HR = 1.78; 95% CI 1.32–2.39; $p < 0.001$) [27, 28]. Interestingly, insulin promotes genomic instability, via DNA damage [29•] which may provide a target for cancer prevention and treatment interventions.

Impact of Obesity on Response to Systemic Therapy

In addition to fostering a pro-tumorigenic state, obesity also confers diminished response to several standard anticancer treatments including chemotherapy and endocrine therapies. BC survivors with obesity have higher risks of recurrence even in those who have attained a pathologic complete response (pCR) after neoadjuvant therapy, where obese patients who achieved pCR had a shorter invasive disease-free survival (IDFS) compared to non-obese patients (HR = 2.46; 95% CI 1.13–5.35) [30•]. However, no significant associations have been observed between BC subtype and OS in obese patients who achieved pCR [30•].

Endocrine Therapy

Increased levels of estrogen and secretion of cytokines and adipokines are linked to the promotion of therapeutic resistance [31]. Patients with MetS were found to have a 1.4-fold greater risk of endocrine resistance, where post-treatment

Ki67 was used as a surrogate marker of endocrine therapy response [32••]. A retrospective analysis of 53,816 women who received therapy for early BC in accordance with Danish Breast Cancer Cooperative Group protocols between 1977 and 2006 indicated that endocrine therapy was less effective after 10 years in obese patients, with an increased risk of death from all causes (HR = 1.57; 95% CI 1.09–2.26). The primary endocrine therapy used in this study was tamoxifen with a duration ranging from 1 to 5 years, with aromatase inhibitor (AI) as the second most frequently used endocrine therapy [33].

In post hoc exploratory analyses of randomized trials, tamoxifen had similar efficacy regardless of BMI, while obesity has been associated with reduced efficacy of AIs. In an exploratory analysis of the NSABP B-14 trial, patients with hormone receptor-positive BC and node negative disease derived benefit from tamoxifen regardless of BMI with reductions in BC recurrence and overall mortality. Patients receiving tamoxifen had a 40% reduction in BC recurrence and 23% reduction in overall mortality compared to placebo which did not vary across BMI groups ($p = 0.34$ and 0.43, respectively) [34]. Exploratory analyses of the ABCSG-12 and ATAC trials also indicate that tamoxifen efficacy is not modified by BMI, whereas the efficacy of AI for reducing BC recurrence in postmenopausal women is compromised by obesity. Specifically, in the ABCSG-12 trial, patients who received tamoxifen had no significant difference in disease-free survival (DFS) (HR = 0.94; 95% CI 0.60–1.64; $p = 0.76$) and OS (HR = 0.83; 95% CI 0.35–1.93; $p = 0.65$) according to BMI. However, patients who were overweight or obese and received anastrozole had increased risk of recurrence (HR = 1.53; 95% CI 1.01–2.31; $p = 0.04$ and death (HR = 1.93; 95% CI 1.04–3.58; $p = 0.03$) compared to patients with normal weight [35]. In the ATAC trial, women who received tamoxifen had similar recurrence rates across all BMI groups when compared to the lowest quintile, while postmenopausal women with a BMI > 30 kg/m^2 who received anastrozole had increased risk of recurrence (HR = 1.60; 95% CI 1.06–2.14) [36]. Notably, in the Breast International Group 1–98 trial, the treatment effect of letrozole did not differ according to BMI (treatment by BMI interaction $p = 0.74$) [37]. For now, aromatase inhibitors remain the standard endocrine therapy in postmenopausal women; however, prospective trials are needed to test other endocrine approaches such as novel oral selective estrogen receptor degraders/downregulators in the setting of obesity.

The reduced efficacy of AIs observed in overweight and obese populations is thought to arise from various mechanisms, including adipokine imbalance favoring leptin overproduction which in turn promotes acquired resistance to AI via the leptin signaling pathway [38]. Other contributing mechanisms include increased adipose stromal cell production of aromatase which could overwhelm the potency of pharmacologic inhibition [39]. Consistently, suppression of serum estradiol levels is less efficient in obese patients treated with AI versus normal weight patients, although suppression of estradiol levels is greater with letrozole than anastrozole across BMI ranges [40, 41]. Whether AI dose intensification or modification can overcome these effects is currently unclear, and clinical trials are needed to test this hypothesis.

Chemotherapy

Standard chemotherapy dosing is based on estimated body surface area (BSA). Due to safety concerns, chemotherapy doses were historically capped at a BSA of 2.0 m^2 or adjusted to ideal body weight; however, several studies have demonstrated inferior outcomes when doses are capped for obese patients. In the CALBG 8541 trial, obese patients treated with adjuvant cyclophosphamide, doxorubicin, and fluorouracil doses according to ideal body weight had inferior outcomes with increased recurrence rates compared to those doses according to actual body weight (risk ratio (RR) = 0.73; 95% CI 0.53–1.00) [42]. The PANTHER phase III trial compared tailored dosing of adjuvant epirubicin, cyclophosphamide, and docetaxel according to hematological nadirs vs. standard interval dosing based on BSA in early BC. Exploratory analyses showed a trend of improved recurrence-free survival for obese patients with the tailored approach (HR = 0.49; 95% CI 0.26–0.90), but this was not statistically significant when compared to the non-obese cohort (HR = 0.79; 95% CI 0.60–1.04; $p = 0.175$). No significant difference in toxicity was observed between different BMI groups [43]. Based on these and other similar data, current guidelines from the American Society of Clinical Oncology (ASCO) recommend full weight-based dosing and have noted that there is no evidence of increased toxicity among obese patients who received full weight-based chemotherapy [44].

Even with appropriate dosing, obese patients have worse BC outcomes after treatment. BSA-based formulations do not take body composition into account and thus may not accurately reflect drug distribution and pharmacokinetics in obese patients [45]. An exploratory analysis of the adjuvant BIG 2–98 trial found increased risk of recurrence (HR = 1.12; 95% CI 0.98–1.50; $p = 0.21$) and all-cause mortality (HR = 1.32; 95% CI 1.08–1.62; $p = 0.007$) with increasing BMI in the docetaxel containing arm, whereas outcomes were not impacted by BMI in the non-docetaxel arm. This differential effect of BMI may be related to the lipophilic properties of taxanes, which promotes higher affinity to adipose tissue leading to sequestration and decreased tumor delivery [46••]. Accordingly, future risk stratification paradigms could account for obesity-mediated response to specific cancer therapies.

Anti-HER2 Targeted Therapy

Preclinical data indicate that obesity affects the pharmacokinetic availability of anti-HER2 monoclonal antibodies like trastuzumab, including reduced plasma concentrations and potentially less clinical benefit [47]. However, since anti-HER2 targeted therapies are conventionally given alongside chemotherapy or endocrine therapy in the treatment of BC, it is difficult to separate the possible clinical impact of obesity specific to anti-HER2 therapy in humans. The impact of obesity on tyrosine kinase inhibitor efficacy in HER2 + BC is unclear, though it is notable that an exploratory analysis of the neoALTTO trial of neoadjuvant paclitaxel/trastuzumab + / − lapatinib demonstrated that obese patients with hormone receptor-positive tumors were less likely to achieve pCR after neoadjuvant therapy compared to normal weight patients (odds ratio 0.56; 95%CI 0.31–1.01; $p = 0.054$) [48•]. In an exploratory analysis of the ALTTO BIG 2–06 trial (where some treatment arms included lapatinib in the adjuvant setting), obese patients had significantly increased risk of recurrence (HR 1.25; 95% CI 1.04–1.50) and all-cause mortality (HR 1.25; 95% CI 1.18–2.84). Weight loss of ≥ 5% was also noted to be associated with decreased survival, although diarrhea is a known adverse effect of lapatinib and weight loss may have been an indicator of increased treatment toxicity leading to treatment discontinuation [49•, 50].

In the metastatic setting, some observational studies have suggested a favorable effect of obesity in HER2 + BC. In this potential "obesity paradox," elevated BMI is associated with greater risk of BC diagnosis and recurrence, whereas after the development of metastatic disease, obesity is paradoxically associated with improved survival compared to normal BMI in some studies. For example, in a pooled analysis of patients with metastatic HER2 + BC, BMI in the obese range was significantly associated with improved OS compared to normal BMI (HR 0.82; 95% CI 0.72–0.95); this observation was independent of hormone receptor status [51•]. One potential explanation for this paradox may be that in advanced metastatic BC, low nutritional reserve and cancer cachexia contribute to poor outcomes. However, adjustment for performance status and albumin level did not modify the association between elevated BMI and improved survival in this metastatic population. Further research and careful disease and host phenotyping are needed to delineate the influence of BC and TME biology, effects of BC treatment, and impact of body composition and other nutritional indicators.

Lifestyle Interventions and Breast Cancer Recurrence

Several clinical trials have investigated lifestyle interventions for weight loss among BC survivors, mostly among women with early BC who have completed initial cancer treatment (surgery, radiation therapy, adjuvant chemotherapy). Modalities of intervention encompass in-person individual or group sessions [52–54], print-based personalized recommendations [55], phone-based counseling [56], or combinations of the above methods [57–61].

While most of these studies showed promising results in achieving significant weight loss and BMI reduction, only a subset examined the effect of such interventions on BC recurrence and survival outcomes with mixed results (Table 1). In the Women's Intervention Nutrition Study (WINS), which tested dietary fat reduction via telephone-based counseling in a cohort of 2437 women with resected early BC, mean body weight was significantly lower in the low-fat diet group compared to control group, with a difference of 2.7 kg (95% CI 0.9–4.5; $p = 0.005$), and relapse-free survival (RFS) was improved (HR 0.76; 95% CI 0.60–0.98; $p = 0.034$) at 5 years [62]. Interestingly, the dietary fat reduction intervention appeared to have a greater effect on RFS among women with hormone receptor negative BC (HR 0.58; 95% CI 0.37–0.91) than those with hormone receptor-positive disease (HR 0.85; 95% CI 0.63–1.14), though the interaction was not statistically significant [62]. In the Lifestyle Intervention in Adjuvant Treatment of Early Breast Cancer (LISA) study, which included 338 postmenopausal women with hormone receptor-positive BC, telephone-based behavioral counseling did not improve DFS (HR 0.71; 95% CI 0.41–1.23; $p = 0.23$) or OS (HR 0.86; 95% CI 0.35–2.14; $p = 0.74$) at a median follow-up of 8 years despite a mean weight loss of 3.1 kg (3.6%) in the intervention group vs 0.3 kg (0.4%) in the control group at 24 months ($p < 0.001$), although this trial was closed early and may have been underpowered for survival endpoints [56, 63]. In the Women's Healthy Eating and Living (WHEL) trial, which assessed a telephone-based counseling program with cooking classes in a cohort of 3088 women with stage I–III BC, there were no significant differences in change in body weight, event-free survival (HR 0.96; 95% CI 0.80–1.14; $p = 0.63$), or OS (HR 0.91; 95% CI 0.72–1.15, $p = 0.43$) between the intervention and control arms [59].

The inconsistent findings from these trials raise the possibility that dietary interventions may affect subgroups of BC survivors differently, and their impact on recurrence and survival outcomes may be mediated by effective weight loss. It is possible the lack of effect on survival outcomes in the WHEL trial may be attributable to the

Table 1 Randomized controlled trials evaluating effects of lifestyle interventions on recurrence and survival among early breast cancer patients

Trial	Patient cohort	Cohort size	BMI (kg/m^2)	Intervention	Primary endpoint	Outcomes	Weight change
Completed							
WINS [62]	Resected, early-stage BC within 365 days of surgery (enrolled 1994–2001)	2437	All	Individual dietician counseling on low-fat eating plan, optional monthly group sessions	RFS	24% lower risk of relapse in intervention vs control group at 5 years RFS (HR = 0.76; 95% CI 0.60–0.98, $p = 0.034$ for adjusted Cox model analysis) ER-neg (HR = 0.58; 95% CI 0.37–0.91); ER-pos (HR = 0.85; 95% CI 0.63–1.14)	Significantly lower mean body weight in intervention vs control group at 5 years, with difference of 2.7 kg (95% CI 0.9–4.5; $p = 0.005$)
LISA [56, 63]	T1-3, N0-3, M0 hormone receptor-positive postmenopausal BC receiving adjuvant letrozole (enrolled 2007–2009)	338	≥ 24	Telephone-based counseling	DFS	No significant effect on DFS (HR = 0.71; 95% CI 0.41–1.24, $p = 0.23$)	Significant weight loss ($p < 0.001$) in intervention vs control group (− 5.3% vs − 0.6% at 6 months, − 5.5% vs -0.6% at 12 months, − 3.7% vs − 0.4% at 24 months)
WHEL [59]	Stage I–IIIA BC diagnosed within 4 years who have completed primary treatment (enrolled 1995–2000)	088	Any	Telephone-based counseling with cooking classes, monthly newsletters	EFS	No significant effect on EFS (HR = 0.96; 95% CI 0.80–1.14; $p = 0.63$) or OS (HR = 0.91; 95% CI 0.72–1.15; $p = 0.43$)	No significant change in body weight in intervention group at any time point No significant between-group difference in body weight
DIANA-5 [64, 65]	Stage I–III BC diagnosed within 5 years who have completed initial treatment	1542 (actual)	Any	In-person dietary counseling, monthly exercise classes	Recurrence	No significant effect on recurrence (HR 0.99, 95% CI 0.69–1.40). In a secondary analysis, the upper tertile of dietary index change had lower risk of recurrence (HR 0.59; 95% CI 0.36–0.92)	Significant difference between intervention group and control in weight loss (− 2.4 kg vs − 0.9 kg, $p < 0.001$), BMI reduction (− 1.0 vs − 0.4, $p < 0.001$), and decrease in waist circumference (− 2.6 cm vs − 1.0 cm, $p < 0.001$) at 1 year
Follow-up ongoing							
PREDICOP [66]	Stage I–IIIA BC within 3 months of completing primary treatment	2000 (estimated)	18–40	In-person dietary and exercise counseling	Recurrence rate	N/A	

Table 1 (continued)

Trial	Patient cohort	Cohort size	BMI (kg/m^2)	Intervention	Primary endpoint	Outcomes	Weight change
SUCCESS C [67]	Early-stage HER2- BC within 6 weeks of surgery	2292	24–40	Telephone-based individualized lifestyle intervention	DFS	N/A	Significant weight loss in the intervention (mean − 1.0 kg; 95% CI − 60 to − 1.39) *vs* control group. No difference in DFS or OS in an exploratory interim analysis
BWEL [68••, 69]	Stage II–III HER2- BC within 12 months of diagnosis and > 21 days from completing primary treatment	3177 (actual enrollment)	≥ 27	Telephone-based individualized lifestyle intervention	IDFS	N/A for IDFS	Significant weight loss ($p < 0.0001$) in intervention (− 4.4 kg, − 4.8%) *vs* control arm (+0.7 kg, +0.9%) at 12 months

BC breast cancer, *RFS* relapse-free survival, *HR* hazard ratio, *CI* confidence interval, *DFS* disease-free survival, *ER* estrogen receptor, *EFS* event-free survival, *HER2* human epidermal growth factor receptor 2, *IDFS* invasive disease-free survival, *N/A* not available, *OS* overall survival, *vs* versus

lack of significant weight loss when compared to WINS, a study with a comparable sample size in which dietary intervention led to significant weight loss and improvement in RFS. Differences in cohort baseline characteristics between WINS and WHEL, such as age and menopausal status, time between diagnosis and enrollment, and severity of disease may also account for the discrepant findings [70]. The WINS cohort included women aged 48–79 years, within 1 year of diagnosis, and over half had stage 1 disease; the WHEL trial enrolled women aged 18–70 years, within 4 years of diagnosis, and only about one-third had stage 1 disease. These differences suggest that dietary interventions may impact BC survivors differently based on age at diagnosis, timing of intervention, and disease severity. Further research is needed to elucidate the possible differential effects of lifestyle interventions on various subgroups of BC survivors.

More recently, the ongoing Breast Cancer Weight Loss (BWEL) trial reported the effects of a telephone-based intervention promoting caloric restriction and increased physical activity on weight loss among 2393 women with stage 2–3 HER2 negative BC. Interim analysis demonstrated a significant difference in percent weight change in the intervention group compared to control (− 4.8% vs + 0.8%, $p < 0.0001$) at 12 months [68••]. Increased weight reduction was observed in the intervention group compared to control across demographics and tumor characteristics [68••]. The intervention led to greater weight loss among post-menopausal compared to pre-menopausal women (− 6.39% vs − 4.68%, interaction $p = 0.004$) and among non-Black and non-Hispanic individuals (− 6.05%) compared to Black (− 3.74%) and Hispanic (− 4.13%) groups (interaction $p = 0.018$) [68••]. Whether the intervention will lead to a significant difference in IDFS, the study's primary endpoint remains to be seen.

These and other trials have established the feasibility of lifestyle and weight loss interventions in BC survivors. However, further investigation is needed to elucidate the impact of lifestyle modification on BC outcomes. Our group has previously recommended a precision medicine approach to testing diet and lifestyle strategies, including highly controlled interventions using metrics adapted from drug development starting with early phase dose-finding trials to phase 3 efficacy trials with classical oncologic endpoints [71]. The use of precision lifestyle interventions, such as personalized exercise prescriptions and pre-prepared meal delivery, provides rigorous assessment of impact on key biologic pathways contributing to treatment resistance and tumor growth. For example, in an ongoing study, our group is testing the impact of an individualized energy-restricted plant-based diet plus exercise prescription during adjuvant AI therapy on aromatase levels, inflammation, and other key biologic pathways within breast tissue [72]. These findings will be used to identify predictors of response, effective dosing of

caloric restriction and exercise, and inform the design of phase 3 trials with survival endpoints. Highly controlled lifestyle interventions, if successful, could ultimately be adapted into implementable behavioral interventions, such as telephone counseling, that incorporate relevant biomarkers of response. By inverting the current paradigm of testing broad behavioral interventions, a stepwise approach starting with high fidelity diet and exercise therapies could provide new data and insights for prescribing lifestyle intervention with similar precision as anti-cancer therapies. Multiple ongoing randomized controlled trials will seek to further elucidate the impact of lifestyle interventions on recurrence and survival outcomes which are summarized in Table 1.

Pharmacological and Surgical Interventions for Obesity and Breast Cancer

Type 2 diabetes mellitus (T2DM) and other metabolic syndrome disorders have been associated with increased risk of cancer recurrence through similar pathways as in obesity which includes inflammation, insulin resistance, and protumorigenic changes in the TME. These observations have led to investigations of metformin and other anti-diabetic agents as well as bariatric surgery in patients with BC [73].

Drug Therapy

Metformin is one of the most widely studied anti-diabetic agents in BC. Metformin is a biguanide which acts by increasing insulin sensitivity and decreasing hepatic glucose output; it can induce modest weight loss and has been associated with potential beneficial effects against BC in observational and preclinical studies [74•, 75]. Small prospective trials in BC survivors noted improved levels of biomarkers associated with BC outcomes such as serum estradiol, leptin, and serum insulin [76•, 77]. An exploratory analysis of the ALTTO trial found that metformin improved DFS (HR 1.40; 95% CI 1.01–1.94; $p = 0.043$) and OS (HR 1.87; 95% CI 1.23 to 2.85; $p = 0.004$) in patients with hormone receptor and HER2 + disease and diabetes. Patients with diabetes were more likely to have a BMI ≥ 30 kg/m^2 and larger primary tumors ($p < 0.001$) [78].

On the basis of promising observational and pilot data, the randomized phase III MA.32 trial was designed to test the effects of adjuvant metformin versus placebo on IDFS in patients with early BC and no diagnosis of diabetes. After enrollment of 3643 patients, futility was declared for patients with hormone receptor negative BC, and the primary analysis was conducted for 2533 patients with hormone receptor-positive BC. The median BMI was 27 kg/m^2 with an interquartile range of 24–32 kg/m^2. The incidence rates for IDFS were 2.78 per 100 patient-years in the metformin group vs 2.74 per 100 patient-years in the placebo group (HR 1.01; 95% CI 0.84–1.21; $p = 0.93$). OS as a secondary endpoint was also not significantly different between groups with an event rate of 1.46 per 100 patient-years in the metformin group vs 1.32 per 100 patient-years in the placebo group (HR 1.10; 95% CI 0.86–1.41; $p = 0.47$) [79••]. These negative findings suggest that the metabolic changes and any potential direct antitumor effects of metformin were insufficient to significantly affect BC outcomes. Other potential contributors to the lack of significant impact on IDFS include advances in BC treatments over the past two decades that may have outweighed potential benefits of adding metformin, exclusion of patients with known diabetes or fasting glucose of > 126 mg/dL, and low enrollment of Hispanic or African American populations who have higher rates of hyperinsulinemia and worse BC outcomes [80].

The MA.32 trial and other key randomized trials are summarized in Table 2 and have not shown definitive improvement in pCR or IDFS with the use of metformin in early BC. Glucagon-like peptide-1 receptor agonists (GLP-1RA) are a novel class of medications for weight management that delay gastric emptying, promote satiety, and improve insulin sensitivity [81]. The mean weight reduction with use of these agents is 8–15% of baseline body weight, with 63–86% of patients achieving ≥ 5% reduction in body weight and 33–69% achieving ≥ 10% [82–84]. Preclinical studies of GLP-1RA have shown promising anti-tumor activity in breast cancer cell lines via cancer cell apoptosis and inhibition of proliferation [85, 86]. Prospective clinical trials testing GLP-1RAs in patients with breast cancer powered for breast cancer outcomes are needed.

Bariatric Surgery

There are limited data available on the role and impact of bariatric surgery in reducing BC recurrence. Observational data from the primary risk reduction setting support the hypothesis that bariatric surgery may be an effective strategy for reducing BC recurrence. Bariatric surgery offers sustained weight loss in patients with obesity, leading to improvements in insulin resistance and inflammation. The four main procedures of bariatric surgery include adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, and bilio-pancreatic diversion. The type of procedure chosen is determined by patient characteristics (e.g., BMI and co-morbidities) and potential procedural risks [90]. Bariatric surgery recommendation criteria include having a BMI ≥ 35 kg/m^2, the presence of both T2DM and BMI ≥ 30 kg/m^2, or BMI 30–34.9 kg/m^2 refractory to medical interventions [91].

In observational studies, bariatric surgery is associated with a decreased risk of developing hormone receptor-positive BC in obese patients (HR 1.38; 95% CI 1.21–1.58)

Table 2 Randomized trials evaluating the use of metformin in early breast cancer

Study designation	Phase	N	Intervention	Breast cancer subtypes	Primary endpoint	Primary outcome achieved
MA.32 [79••]	3	2533	Adjuvant metformin vs placebo	Hormone receptor-positive patients only	IDFS	No IDFS events were 2.78 per 100 patient-years in the metformin group and 2.74 per 100 patient-years in the placebo group (HR = 1.01; 95% CI 0.84–1.21; $p = 0.93$)
METTEN [87]	2	84	Neoadjuvant FEC-TH +/− metformin	HER2 positive patients only	pCR	No pCR rate was 65.5% in metformin-containing arm compared with 58.6% in the control arm (OR = 1.34; 95% CI 0.46–3.89; $p = 0.59$)
NeoMET [88••]	2	92	Neoadjuvant DEC +/− metformin	Any	pCR	No pCR rate was 14.6% in the in metformin-containing arm compared with 12.5% in the control arm ($p = 0.78$)
I-SPY2 [89•]	2	234	Neoadjuvant paclitaxel +/− metformin/ganitumab	HER2 negative patients only	pCR	No pCR rate was 22% in the in metformin-containing arm, compared with 16% in the control arm. Did not meet prespecified threshold for further investigation in a phase 3 trial

CI confidence interval (CI), *DEC* docetaxel, epirubicin, cyclophosphamide, *FEC-TH* fluorouracil, epirubicin, cyclophosphamide, paclitaxel, trastuzumab, *HR* hazard ratio, *HER2* human epidermal growth factor receptor 2, *IDFS* invasive disease-free survival, *n* number, *OR* odds ratio, *pCR* pathological complete response

[92, 93•]. The SPLENDID trial was an observational, matched cohort study which reported that the incidence of any obesity-associated cancer (including postmenopausal BC) at 10 years among obese adults was 2.9% in the bariatric surgery group versus 4.9% in the nonsurgical control group (HR 0.68; 95% CI 0.53–0.87; $p = 0.002$) [94••]. In a recent meta-analysis, bariatric surgery was associated with a significant reduction in the risk of developing BC of all subtypes (pooled RR 0.56; 95% CI 0.44–0.71; $p < 0.01$) and improved cancer-specific mortality (RR 0.51; 95% CI 0.42–0.62; $p < 0.01$) [95]. Limited data suggest a protective effect of bariatric surgery in the post-diagnosis setting as well. In a case series including 13 women who completed definitive treatment for early BC, bariatric procedures were well tolerated and induced an average weight loss of 28.2% at 2 years [96]. Only one patient experienced BC recurrence at a median follow-up of 11.7 years and 5.3 years after bariatric surgery. Clinical trials in this setting are now being planned, such as the randomized phase II BariaTric Surgery After Breast Cancer Treatment (BATS) trial [97]. The initial observational findings support the rationale for clinical trials testing bariatric surgery as a strategy to reduce BC recurrence in the setting of severe or refractory obesity.

Beyond BMI: Adiposity as an Indicator of Metabolic Risk

Although BMI is currently the standard metric used to diagnose obesity, its limitations as a predictor of individual cardiometabolic risk are well documented [98]. As an anthropometric index based on height and weight, BMI does not account for the effects of age, menopausal status, sex, fat distribution, or muscle mass, but rather provides an indirect estimate of body fat that is neither sensitive nor specific [99]. Recent research has identified subgroups of individuals with normal BMI who experience adverse health consequences similar to those with obese-range BMI, including excess body fat, dyslipidemia, insulin resistance, elevated blood pressure, and low-grade inflammation [100–102]. This condition, known as metabolic obesity in normal weight, has been associated with increased risk of numerous cancers

typically associated with classical obesity [103•, 104, 105], including post-menopausal BC [106].

Recent investigations have shown that body composition parameters, particularly central adiposity, are associated with elevated risk of post-menopausal BC among non-obese individuals across ethnicities [103•, 107–110]. In studies using direct quantification methods for body composition, such as bioelectrical impedance analysis or dual-energy X-ray absorptiometry, total body and trunk fat mass are associated with increased risk of postmenopausal BC among non-obese women [104, 107]. Increased trunk fat is also associated with altered metabolic biomarkers such as elevated insulin, triglycerides, and lower high-density lipoprotein cholesterol, consistent with metabolic dysfunction in this subgroup [107]. These findings raise the concern that reliance on BMI as a risk stratification tool may provide false reassurance by excluding normal-weight individuals with excess body fat who would benefit from risk reduction interventions. Further investigation is needed to better characterize the effect of body composition and increased adiposity on BC recurrence, and prospective clinical trials should consider inclusion of this population.

Conclusion

Obesity has reached pandemic proportions and increases the risk of recurrent BC. The pro-tumorigenic effects of obesity occur at both the local level via adipose dysfunction and alterations in the TME, as well as systematically via circulating inflammatory and metabolic mediators. Concerted efforts are underway globally to improve patient education regarding healthy lifestyle choices to reduce obesity rates; however, precise guidelines and prescribed lifestyle optimization plans are likely to be more successful than generic counseling in terms of adherence and anti-cancer efficacy. Incorporation of metabolic status using more precise metrics than BMI may also improve risk stratification for BC recurrence, and future research is needed to test whether this approach should modify BC treatment selection. The development of lifestyle interventions using a precision medicine paradigm may help to more efficiently and accurately select effective dietary and exercise interventions, which could be further augmented by pharmacologic approaches with metabolic targets that are relevant to cancer growth factor pathways. Ultimately, it is clear that obesity and metabolic dysfunction need to be clinically addressed in the setting of a cancer diagnosis to improve cancer-specific outcomes and overall mortality in cancer survivors.

Abbreviations AI: Aromatase inhibitors; BC: Breast cancer; BMI: Body mass index; CI: Confidence interval; DFS: Disease-free survival; HR: Hazard ratio; HER2: Human epidermal growth factor receptor 2; IGF-1: Insulin-like growth factor-1; IDFS: Invasive disease–free survival; MetS: Metabolic syndrome; OS: Overall survival; pCR: Pathological complete response; EFS: Relapse-free survival; RR: Risk ratio; TME: Tumor microenvironment; TNF-α: Tumor necrosis factor-α; T2DM: Type 2 diabetes mellitus

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Declarations

Competing Interests The authors declare no competing interests.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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