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Obesity, Metabolic Syndrome, and Breast Cancer: From Prevention to Intervention

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Abstract

Obesity contributes to an estimated forty-percent, or 630,000 cases, of malignant neoplasms diagnosed in the United States[1] and higher body mass index (BMI) has been associated with at least seventeen types of solid tumors, including 9% of all breast cancer cases. In this review, we discuss the impact of obesity and consequences of obesity, including the metabolic syndrome and type 2 diabetes mellitus, on breast cancer risk and recurrence. Recent work has identified multiple molecular mechanisms that may underlie the association between obesity and breast cancer. In particular, insulin resistance, increased inflammatory cytokines, leptin signaling, and adipokine signaling have been shown to affect breast cancer risk and outcomes. While obesity is associated with higher breast cancer incidences and worse breast cancer outcomes, several risk reduction methods have been shown to attenuate these risks. Both metformin and statins have been shown to improve disease free survival and overall survival compared to non-users. Metformin also has been associated with lower risk of breast cancer incidence. Furthermore, increased physical activity and weight loss have been shown to decrease risk of breast cancer, especially in post-menopausal women. These studies have emphasized the potential impact that lifestyle changes can have on breast cancer risk and outcomes, and demonstrate the need for randomized control trials to evaluate the roles of metformin and statins for the treatment and chemoprevention of breast cancer.

I. Introduction

Although much attention has been focused on the genetic risk factors for breast cancer, only around 10 - 20% of all breast cancer cases are attributable to genetic predisposition [2]. Most cases of breast cancer are considered sporadic, in which there are no known genetic mutation or family history. Studies have attempted to elucidate extrinsic risk factors that give rise to sporadic breast cancer. A clinical entity termed metabolic syndrome associated with obesity has been shown to contribute to an estimated of 630,000 cases or 40% of all

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Conflicts of Interest

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malignant neoplasms including breast cancer diagnosed in the United States [1]. Higher body mass index (BMI) has been associated with at least seventeen types of solid tumors, including nearly a fifth of breast cancers, particularly in the post-menopausal setting [3]. Given that many of the risk factors associated with metabolic syndrome are modifiable, this has become a major area of focus to develop strategies to prevent breast cancer and improve breast cancer outcomes. One study has estimated that more than 30% of breast cancer can be prevented with lifestyle changes [4].

In this review, we will summarize the impact of obesity and type 2 diabetes mellitus associated with metabolic syndrome on breast cancer risk and outcomes. We next discuss some of the proposed molecular mechanisms of metabolic syndrome focusing on adipokine signaling, cellular metabolism and stromal contribution. Finally, we examine the data supporting the use of clinical interventions, both through conservative lifestyle measures such as exercise and diet and through pharmacologic intervention, to treat obesity and diabetes. Lifestyle modifications such as exercise, weight loss to combat obesity and the use of commonly prescribed medications to combat diabetes or hypercholesterolemia may result in a favorable “bystander” effect in improving breast cancer outcomes.

Metabolic Syndrome and Breast Cancer

The metabolic syndrome is classically defined as having three or more of the following: central obesity (waist circumference of more than 35 inches for women), hypertension (blood pressure >130/85 mmHg), insulin resistance (fasting glucose >110 mg/dL), low HDL cholesterol (<50) and high triglycerides (>150 mg/dL). Though each individual component of the metabolic syndrome is independently associated with breast cancer, a large retrospective study by Osaki et al has shown that the constellation of factors in metabolic syndrome increases the risk for breast cancer by 2.87 times (95% C.I. 1.67-4.94), among Japanese women [5]. The relative impact of the metabolic syndrome on breast cancer risk was even higher in post-menopausal women (HR 6.73, 95% C.I. 2.93-15.43). Similar results were also seen in a meta-analysis conducted by Bhandari et al., who found that metabolic syndrome increased the relative risk (RR) of breast cancer by 47% (95% C.I. 1.15-1.87)[6].

Obesity: a mounting epidemic

The most recent results from the National Health and Nutrition Examination Survey showed that 68.8% of U.S. adults 20 years or older were overweight or obese, with 35.7% of Americans being obese (body mass index (BMI) >30) [7]. In contrast, only 56% of U.S. adults from two decades ago were considered overweight or obese.

In the UK, it has been estimated that 9% of all breast cancer cases are attributed directly to obesity [8]. In the United States, a key prospective cohort analysis of women from the Nurses' Health Study has demonstrated that weight gain was associated with an increased risk of breast cancer [9]. Over 49,000 postmenopausal women who did not have a history of cancer at the start of the study were followed for up to 24 years. In total, 4393 cases of invasive breast cancer were documented. Compared to women who maintained their weight, women who had gained 25.0 kg or more since 18 years of age had a 45% increased risk of breast cancer (95% confidence interval (C.I.) 1.27-1.66, $p<0.001$). Similarly, compared to

weight maintenance, women who gained 10.0 kg or more since menopause are 18% more likely to have invasive breast cancer (95% C.I. 1.03-1.35, $p=0.002$).

As obesity is a modifiable contributor to the metabolic syndrome and that obesity is on the rise, with every two out of three Americans being overweight or obese in 2014[10], strategies to reduce obesity will have long-term consequences that extend far beyond morbidities associated with metabolic syndrome which include reduction of cancer incidence and improvement of cancer outcomes.

Type 2 Diabetes Mellitus

Among the components of the metabolic syndrome, the association between type 2 Diabetes and insulin resistance with respect to cancer risk and cancer outcomes has been extensively explored. The Centers for Disease Control and Prevention (CDC) has estimated that up 30.3 million Americans have diabetes and, 84.1 million people (33.9% of the population) are pre-diabetic [11]. The rising incidence of type 2 diabetes has important implications because it has been shown to increase the risk of nearly every solid tumor[12]. One meta-analysis has shown that women with diabetes had a 20% increased risk of breast cancer compared to women without diabetes [13]. Another meta-analysis that included 40 studies estimated that type 2 diabetes increases the risk of breast cancer by 27% (95% C.I. 1.16-1.39). The risk was significantly increased even after adjusting for BMI (RR 1.16, 95% C.I. 1.08-1.24), demonstrating that diabetes is an independent risk factor for breast cancer [14].

Furthermore, the impact of insulin resistance on the risk of breast cancer appears to be more significant in post-menopausal women than pre-menopausal women [15]. In a large prospective study within the Nurses' Health Study, postmenopausal women with type 2 diabetes were 17% more likely to have breast cancer than women without diabetes (95% C.I. 1.01-1.35), even after controlling for factors like age, obesity, family history of breast cancer, physical activity level and alcohol consumption. Most studies have not shown a clear impact of obesity or insulin resistance on the incidence of pre-menopausal breast cancer, largely in part due to the fact that a significant proportion of early breast cancer cases are attributed to genetic risk factors.

II. Molecular mechanisms underlying the connection between obesity and breast cancer

Although there is no single unifying model to account for the complex and systemic effects of obesity and insulin resistance on cancer initiation and progression, several molecular mechanisms have been proposed which include endocrine, autocrine and paracrine signaling pathways as illustrated below[16]. The unique metabolic state associated with adiposity may also have direct and indirect roles in the promotion of cancer. For example, a high energy state may directly propel tumorigenesis and tumor growth by providing increased ATP for increased cell turnover[17,18], and recent evidence for a "metabolic threshold" in a number of cancer types[19,20] have supported the development of targeted metabolic inhibitors as cancer therapeutics.[21]

Hyperinsulinemia and insulin resistance

Obesity has also been shown to cause hyperinsulinemia [22]. In a prospective case-cohort study, breast cancer cases were 2.4 times higher for patients with the highest quartile of fasting insulin levels than those in the lowest quartile. This association was seen in women who were not diabetic or using any hormone therapy.

Adipokine imbalances

Chronic exposure to high fat diet (HFD) and obesity have profound systemic impact on cellular and tissue function and have been thought to promote tumorigenesis through both direct (adipokine signaling and adipose progenitor cells) and indirect (insulin growth factor (IGF) signaling, infiltration of macrophages and dyslipidemia) mechanisms[23]. In addition to adiponectin and leptin which are the two predominant adipose derived hormones, other cytokines including estrogen, tumor necrosis factor (TNF)-alpha, and interleukin (IL)-6 are also secreted by adipose cells and have been implicated as oncogenic factors.

Adiponectin

Adiponectin is a adipokine factor secreted specifically by adipose tissue and is a negative regulator of inflammation and cell proliferation, however in states of obesity, systemic levels of adiponectin drops. Interestingly, low levels of adiponectin or mutations in adiponectin or adiponectin receptors resulting in decreased adiponectin signaling appears to correlate with increased risk of multiple human cancer types[24]. Thus, it is thought that adiponectin has antineoplastic activity, supported by evidence at least in murine cancer models where the administering of adiponectin appears to reduce cellular proliferation, vascularity, and tumor invasion.[25]

Leptin

In states of chronic obesity, the overabundance of leptin, a hormone made by adipose cells that regulates energy balance, appears to initiate a pro-inflammatory cascade by inducing the secretion of IL-1, IL-6, IL-12, and TNF α by innate immune cells and enhancing reactive oxygen species (ROS) production[26,27]. The impact of leptin in promoting tumor progression is especially well-supported. For example, obese mice with higher leptin levels are more susceptible to azoxymethane-induced colorectal carcinogenesis, and leptin-signaling appears to play a role in mediating HFD-associated lipotoxicity, which induces precancerous lesions in the gastric epithelium and deregulated expression of stemness genes[28,29]. The leptin receptor gene, *LEPR*, is expressed in multiple solid tumors in humans.[23,30] In addition, mice with deficient peripheral leptin receptor but intact central leptin signaling, showed decreased mammary tumor progression and metastases. Moreover, transplantation of tumors from *LEPR*-deficient mice to wild-type animals resulted in slower tumor growth as compared to transplanted tumors from mice with intact *LEPR* [31]. This is consistent with data in other solid tumor types as well. One study showed that although co-cultured adipocytes promoted the proliferation colon cancer cells, the effect was abrogated in adipocytes from leptin-deficient mice[32].

Increased inflammatory cytokines

Indeed, mounting evidence suggests that obesity may drive the development of cancer indirectly by creating chronic systemic inflammatory state which may be favorable for tumorigenesis by promoting growth factor and cytokine signaling, angiogenesis and cell turnover, or alternatively, by interfering with immune-mediated tumor-cell killing or cancer surveillance[33]. The clinical impact of a chronically dysregulated or impaired immune response is evidenced by an increased incidence of early-onset cancers in patients with autoimmune diseases (e.g. esophageal cancer in patients with gastroesophageal reflux, colorectal cancer in patients with inflammatory bowel disease and celiac disease[34]), and in patients with immune suppression (e.g. Hodgkin's disease and testicular seminoma in patients with HIV/AIDS[35]). In addition, a number of non-mutagenic chemicals are associated with higher cancer risk, possibly by inducing inflammation or immunosuppression[36-38]. Inflammatory tumor promoters may not only act as indirect mutagens through the production of ROS and point mutations (Guanine >Thymine),[36,37] but also can cause an outgrowth of tumors with alternative initiating mutations induced by a primary carcinogen[39,40].

Estrogen

Chronically high estrogen states drive the development and proliferation of mammary cells and consequently has a significant role in promoting hormone-positive breast cancer. [41-43]. Following menopause, the aromatase activity in the adipose tissue compartment is the primary source of estrogen due to conversion of androgen to estrogen and aromatase activity is stimulated by other proinflammatory factors including TNF-alpha and IL-6 as well as IL-1beta. This is exacerbated by the fact that systemic estrogen bioavailability is further elevated due to reduced serum steroid hormone binding globulin, thus resulting in elevated bioavailability of estrogen. Compared to women with normal weight (BMI < 22), obese women (BMI > 30) have 130% higher levels of estradiol[41].

Cancer stem cells

One alternative mechanism through which obesity could drive tumorigenesis is by promoting growth or differentiation of cancer stem cells or progenitor cells which may be mediated by leptin signaling as described above. Of particular interest are the adipose-derived stem cells, which can differentiate into cancer-associated fibroblasts and thereby contribute directly to the tumorigenic effects within the tumor microenvironment. In addition, adipose tissue may contain adult multipotent stem cells which may promote tumor cell invasion, growth or induce angiogenesis.[24]

III. Metabolic Impact on Breast Cancer Survival and Recurrence: Risk and Mitigation

There is strong evidence that mitigating metabolic risk factors may reduce breast cancer recurrences and improved mortality rates. We review evidence of the role of obesity in breast cancer survival and recurrence, highlighting the data from recent clinical studies investigating the impact of lifestyle or medical interventions.

Obesity

While the exact mechanism of how BMI may act to impact breast cancer survival is unclear, some data suggest that BMI is significantly associated with the pathogenesis of breast cancer. For example, higher BMI was shown to be associated with unfavorable breast tumor receptor subtype [44,45]. Obese patients were more likely to be diagnosed with triple negative breast cancer, the most aggressive subtype, and less likely to be diagnosed with luminal A tumors, which in general have better outcomes, compared to normal weight patients. Thus, not only does higher BMI predispose women to tumors with poor outcomes, BMI also affects recurrence and mortality rates independent of tumor subtype.

Despite these studies, conclusive evidence showing direct benefits of weight loss intervention remains unavailable. One ongoing phase III randomized controlled trial (RCT) (Alliance A011401) is evaluating the effect of a 2-year telephone-based weight loss program for women with a BMI of 27 or more who have been diagnosed with stage II-III Her-2/neu (Her-2) negative breast cancer on disease-free survival. The results of this trial will be important to confirm that weight loss has direct benefits with regard to outcomes after breast cancer diagnosis.

Physical activity

Similar to weight loss, increased physical activity may also decrease recurrence and mortality rates in women diagnosed with breast cancer [46-48]. As summarized in Table-1, these studies support the benefits of physical activity on breast cancer outcomes independent of weight/BMI. For instance, in the Nurses Health's Study, 2987 female registered nurses diagnosed with stage I, II, or III breast cancer between 1984 and 1998 were mailed questionnaires to assess physical activity levels [46]. Activities included moderate activities, such as walking, hiking, swimming, and dancing, and vigorous activities such as lawn mowing. Every activity was scored using the metabolic equivalent task metric (MET), whereby 3 MET-hours is defined as walking 2 to 2.9 mph for 1 hour. The investigators found that patients who averaged 9 or more MET-hours per week had lower risk of mortality compared to women who did not, and the benefit was especially pronounced in women with hormone positive tumors (RR 0.50, 95% C.I. 0.34-0.74).

Type 2 Diabetes and metformin

Moving beyond lifestyle changes such as weight loss, multiple studies have demonstrated that glycemic control and treatment of metabolic conditions may have a positive impact in breast cancer, as well as many other solid tumors. The risk of recurrence in diabetic women tends to be much higher [49-51]. In a retrospective study by Kaplan et al, there was no statistical difference between diabetic and non-diabetic patients with regards to histological subgroup, grade, hormone receptor status, or tumor size [50]. However, non-diabetic patients had a median disease free survival (DFS) of 81 months, compared to 36 months for diabetic patients. Furthermore, diabetic patients were more likely to have lymph node involvement, a negative prognostic factor ($p=0.013$). In a case-control study by Li et al, it was also found that diabetic patients with estrogen receptor (ER) + breast cancer were 2.2 times more likely to experience a secondary primary contralateral breast cancer (95% C.I. 1.3-3.6) [51]. Furthermore, diabetic breast cancer patients on chemotherapy had higher risk of being

hospitalized for chemotherapy toxicities and higher breast cancer mortality compared to non-diabetic patients (OR 1.38, 95% C.I. 1.23-1.56 and OR: 1.20, 95% C.I. 1.07-1.35 respectively) [52].

Despite the worse outcomes seen in diabetic breast cancer patients, the risk appears attenuated when patients are on metformin therapy[49,53] (Table-3). Sonnenblick et al demonstrated that in HER2+ and HR+ patients, diabetic patients who were not treated with metformin had worse DFS (HR 1.40, 95% C.I. 1.01-1.94, $p=0.043$) and OS (HR: 1.87, 95% C.I. 1.23-2.85, $P=0.004$) compared to those who were treated with metformin[49]. Additionally, recent studies have suggested a beneficial role for metformin in neoadjuvant therapy[54,55]. Jiralerspong et al found that metformin use was independently predictive of pathological complete response (pCR) to neoadjuvant chemotherapy, even after adjusting for BMI, age, stage, grade, receptor status, and taxane use [54]. In fact, metformin users had a significantly higher pCR rate of 24% compared to 16% in non-diabetics and 8% in diabetic patients who were not on metformin ($p=0.02$). Furthermore, Hadad et al conducted a randomized trial for non-diabetic women with operable invasive breast cancer [55]. Patients randomized to receive metformin before surgery showed fewer cells staining for Ki67, a cell proliferation marker, and decreased expression of PDE3B mRNA compared to patients who did not receive metformin, suggesting metformin has an anti-proliferative effect on breast tumor cells.

Whether metformin will benefit non-diabetic breast cancer patients is unknown. Thus, there is a need for randomized control trials to study the role of metformin as adjuvant breast cancer treatment. Currently, there is a phase III RCT by the Canadian Cancer Trials Group (NCT01101438) in which patients with early stage breast cancer are randomized to metformin or placebo for up to 5 years to study disease free survival and overall survival. The results of this trial will be critical in determining whether metformin should be implemented as part of adjuvant breast cancer therapy.

Statins

Statin, a commonly prescribed medication to lower cholesterol, also appear to improve disease-free survival and overall survival[56-60]. Borgquist et al conducted a phase III RCT, which included 8010 post-menopausal women with hormone-positive invasive breast cancer. Although this clinical trial was not intended to evaluate the effects of cholesterol-lowering medications (CLM), the documentation of CLM at the time of randomization to various endocrine therapy treatments made this sub-analysis possible[59]. Patients who used CLMs before or during initiation of endocrine therapy had improved DFS compared to non-users (HR: 0.82, 95% C.I. 0.68-0.99 and HR: 0.79, 95% C.I. 0.66-0.95 respectively).

The benefits of statin use were also illustrated in the Woman's Health Initiative, a large prospective cohort study which followed 146,326 postmenopausal women across 40 US clinical sites for a median of 14.6 years [60]. Compared to patients who were never on statins, patients currently on statins had lower risk of all-cancer death (HR: 0.78, 95% C.I. 0.71-0.86). Other studies were able to demonstrate similar results specifically in breast cancer (Table-2). Murtola et al demonstrated that both pre- and post-diagnostic statin use

was associated with reduced breast cancer mortality (HR 0.46, 95% C.I. 0.38-0.55 and HR: 0.54, 95% C.I. 0.44-0.67 respectively) [57].

While the definitive anti-tumor mechanism of statins has not been established, pre-clinical studies have provided a few hypotheses. Statins have been shown to interfere with the cell cycle, preventing cancer cell proliferation [61]. Furthermore, statins have also been shown to induce apoptosis in many cancer cell lines, including breast cancer cells [62-65]. However, there is a need for large, randomized trials to validate the efficacy of statins as a therapy for breast cancer. For example, there is a phase III RCT (NCT02201381) that is studying the effects of several commonly prescribed medications including atorvastatin, metformin, doxycycline, and mebendazole. While the study will not be completed until 2023, its results will be important for understanding the role of statins in breast cancer therapy.

IV. Interventions in obesity to reduce breast cancer risk

While conventional cytotoxic therapy has a definite role in the treatment and mitigation of cancer, from a public health standpoint, interventions that can prevent obesity-associated cancers are likely as or more important in reducing the economic burden of cancer.

Lifestyle modification

One study estimated that more than 30% of breast cancer cases can be prevented with nutritional modifications and exercise [4,66]. The first aspect of lifestyle modification is weight loss (Table-3). Eliassen et al found that women who lost at least 10.0 kg after menopause, kept the weight off, and never used postmenopausal hormones were 57% less likely to develop breast cancer than those who maintained but did not lose weight (RR 0.43, 95% C.I. 0.21-0.86, P=0.01) [9]. Additionally, a meta-analysis of 20 studies showed that weight loss significantly reduced incidence of breast cancer (OR: 0.82%, 95% C.I. 0.70-0.96)[67].

A second aspect of lifestyle modification is to increase the level of physical activity (Table-1). Multiple studies have found that higher physical activity attenuates the risk of breast cancer [68-71]. However, an estimated 28% of the U.S. population does not participate in the recommended 120 minutes of fitness activities a week. In the Iowa Women's Health Study which followed 41836 postmenopausal women for 18 years and evaluated self-reported level of activity (low, medium and high), high level of physical activity was shown to reduce postmenopausal breast cancer by 14% (RR 0.86, 95% C.I. 0.78-0.96). The impact of physical activity was especially significant in reducing rates of ER + tumors (33%).

One possible mechanism through which physical activity lowers breast cancer risk is through the decrease in circulating levels of estrogen [72]. One study randomized 173 postmenopausal overweight (BMI >24) women who were not on hormone therapy to an exercise regimen or a stretching regimen. The exercise regimen consisted of 45 minutes of moderate intensity activity for 5 days a week for a year. The stretching regiment was once a week for 45 minutes. Even after just 3 months, exercisers had lowered levels of estrone, estradiol and free estradiol (3.8%, 7.7%, and 8.2%), while stretchers had no change or

increased levels ($P = 0.03, 0.07, 0.02$). Women who had lost body fat saw the greatest change in these levels, suggesting the importance of physical activity and maintaining a healthy weight in reducing breast cancer risk.

Chemoprevention beyond selective estrogen receptor modulators (SERMs)

Medical risk reduction traditionally involves selective estrogen receptor modulators (SERMs) such as Raloxifene or Tamoxifen. In the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP), 13,388 women were randomly assigned to receive placebo or tamoxifen for 5 years. After 7 years of follow up, compared to women receiving placebos, those receiving tamoxifen had lower rates of both invasive breast cancer ($RR = 0.57$, 95% C.I. = 0.46-0.70) and non-invasive breast cancer, including ductal carcinoma in situ ($RR = 0.63$, 95% C.I. = 0.45-0.89) [73]. However, there are significant risks of adverse events and intolerable side effects associated with SERMs, including hot flashes, thromboembolisms and endometrial cancer in postmenopausal women.

Because metformin has been shown to improve breast cancer outcomes, there is great interest in using metformin for primary prophylaxis as well (Table-2). Multiple studies have shown that metformin decreases risk of many solid tumors [53,74,75]. One meta-analysis of 28 studies has shown that metformin patients had a pooled relative risk of 0.70 in developing breast cancer compared to non-users (95% C.I. 0.55-0.88) [53]. Bodmer et al used a case-control study and found that diabetic patients on long-term metformin had a much lower risk of breast cancer compared to users on other oral diabetic medication (OR: 0.44, 95% C.I. 0.24-0.82) [74].

However, there is significant heterogeneity in study results for breast cancer. Thus, there are many ongoing randomized clinical trials that attempt to address the role of metformin in primary prevention of breast cancer [76-78]. A phase II RCT (NCT02028221), which is expected to be completed in December 2020, is randomizing overweight or obese premenopausal women with signs of metabolic syndrome to metformin or placebo for 12 months. The primary endpoints are changes in breast density at 6 months and 12 months, which are surrogate markers for breast cancer risk. The results of this study will provide more evidence on whether metformin has the potential to decrease breast cancer risk.

While the use of statins have been shown to be associated with improved breast cancer outcomes, multiple meta-analysis have shown no association between statins and reduced breast cancer incidences [79-81]. Undela et al performed a meta-analysis with 24 studies, which included more than 2.4 million participants and 76,759 breast cancer cases [79]. There was no association found between any statin use and risk of developing breast cancer ($RR: 0.99$, 95% C.I. 0.94-1.04) or long-term statin use and risk of breast cancer ($RR 1.03$, 95% C.I.: 0.96-1.11). Therefore, current evidence does not support the use of statins as a method for medical risk reduction for primary breast cancer prevention.

Conclusion

Obesity and obesity-associated metabolic risk factors significantly impact an individual woman's breast cancer risk and outcomes after diagnosis. Here, we highlighted key literature examining the population-based impact of obesity on breast cancer showing that breast cancer incidence is associated with modifiable risk factors such as obesity, type 2 diabetes and metabolic syndrome. While there is no consensus on the mechanism linking obesity and breast cancer, it appears to involve multiple direct and indirect processes including insulin resistance, increased inflammatory cytokines, proliferation of cancer and adipose stem cells, and adipokine imbalances.

Understanding the mechanisms underlying obesity-associated breast cancer is particularly important because the negative impact of these obesity-associated risk factors on patient outcomes can be attenuated with weight loss through lifestyle changes and conservative medical therapy of the underlying metabolic condition. Weight loss/weight maintenance post-menopause and increased physical activity have been associated with decreased breast cancer incidence, and some studies show promising prophylactic benefit of medical therapy with statins and metformin. Moreover, following breast cancer diagnoses, similar interventions were associated with improved prognosis—weight loss through diet and exercise and the use of metformin and statins in patients with insulin resistance or dyslipidemia are all associated with reduced recurrence and mortality.

In summary, we reviewed this existing literature, which presents a large body of evidence underscoring the importance of metabolic risk factors in breast cancer and that conservative approaches including dietary and lifestyle measures as well as safe and well-tolerated medical therapy of metabolic comorbidities are effective interventions. As current evidence is largely drawn from observational studies, we await the results of over a dozen ongoing randomized clinical trials that are prospectively evaluating the efficacy of these interventions. Coupled with basic and translational work identifying, targetable mechanisms through which obesity and metabolic derangement drive cancer, we are optimistic that promising avenues for clinically actionable metabolic interventions are on the horizon for the treatment of breast cancer.

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*Of importance

** Of major importance

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Table 1

Physical activity

Study	Pubmed ID	Study Population (number of participants)	Follow up (years)	Levels of activity compared	Breast cancer incidence RR (95% C.I.)	Breast Cancer Mortality RR (95% C.I.)	Summary
Bardia et al	17159013	41836	18	2+ vigorous activities or 4+ moderate activities weekly vs. no vigorous or moderate activities weekly	0.86 (0.78-0.96)	NA	Higher physical activity reduces post-menopausal risk of breast cancer, especially ER+/PR- tumors
Kyu et al		174 studies (35 breast cancer specific)		<600 MET-min/week vs. >8000 MET-min/week	0.863 (0.829-0.900)	NA	Attaining higher physical activity levels is associated with lower breast cancer incidence rates
Eliassen et al	20975025	95396 postmenopausal women	>20 yrs	<3 MET-hrs/week vs. >27 MET-hrs/week	HR 0.85 (0.78-0.93)	NA	Even moderate physical activity like brisk walking is associated with lower postmenopausal breast cancer risk
Hardefeldt et al	29223719	139 studies		Physical activity in pre-menopausal women vs none	0.79 (0.72-0.86)	NA	Physical activity is associated with reduced risk of breast cancer, especially if there is high intensity activity
				Physical activity in post-menopausal women vs none	0.82 (0.67-0.97)		
Holmes et al	15914748	2987	8 (median)	3-8.9 MET-hrs/week vs. <3 MET-hrs/week	NA	0.80 (0.60-1.06)	Physical activity post-diagnosis is associated with lower breast-cancer specific mortality
				9-14.9 MET-hrs/week vs. <3 MET-hrs/week		0.50 (0.31-0.82)	
				15-23.9 MET-hrs/week vs. <3 MET-hrs/week		0.56 (0.38-0.84)	
				24+ MET-hrs/week vs. <3 MET-hrs/week		0.60 (0.40-0.89)	
Irwin et al	18711185	933	2	9+ MET-hrs/week vs. 0 MET-hrs/week within 1 year before diagnosis	NA	0.69 (0.45-1.06)	Higher physical activity both pre and post-diagnosis can improved mortality
				9+ MET-hrs/week vs. 0 MET-hrs/week 2 years after diagnosis		0.33 (0.15-0.73)	
Schmid et al	24644304	16 studies		Any increase in physical activity from pre to post diagnosis vs. no change	NA	0.61 (0.46-0.80)	Physical activity both before and after breast cancer diagnosis is associated with reduced breast cancer mortality
				Highest level of physical activity pre diagnosis vs. lowest level of physical activity		0.77 (0.66-0.90)	

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Study	Pubmed ID	Study Population (number of participants)	Follow up (years)	Levels of activity compared	Breast cancer incidence RR (95% C.I.)	Breast Cancer Mortality RR (95% C.I.)	Summary
				Highest level of physical activity post diagnosis vs. lowest level of physical activity		0.72 (0.60-0.85)	

Table 2

Medical management

Study	Pubmed ID	Study Population (number of participants)	Median follow up (years)	Medication compared	Breast cancer incidence (95% C.I.)	Disease-free survival HR (95% C.I.)	Overall Mortality RR (95% C.I.)	Summary
Sonneblick et al	28375706	8381	4.5	No medication vs. Metformin	NA	1.40 (1.01-1.94)	1.87 (1.23-2.95)	Metformin is associated with improved outcomes in diabetic patients
Bodmer et al	20299480	305 case patients, 1153 control patients		Metformin vs. no metformin	Odds ratio 0.44 (0.24-0.82)	NA	NA	Diabetic patients on metformin may have decreased risk of breast cancer
Currie et al	19572116	62809	152,065 person-years	Metformin vs. sulfonylureas	HR 0.98 (0.69-1.41)	NA	NA	Metformin is associated with lower risk of several solid tumors but not statistically significant for breast cancer
				Metformin vs. insulin	HR 1.07 (0.79-1.44)			
Borgquist et al	28380313	8010	Up to 5.5	Statins during tamoxifen therapy vs. no statins	NA	0.79 (0.66-0.95)	NA	Statins may prevent recurrence in HR+ breast cancer
Murtola et al	25329299	31236	3.25	Use of statins before diagnosis vs. no statins	NA	NA	0.54 (0.44-0.67)	Use of statins may have a positive effect on breast cancer survival
				Use of statins after diagnosis vs. no statins			0.46 (0.38-0.55)	
Wang et al	27280630	146326	14.6	Statin users vs. never users			0.60 (0.42-0.85)	Use of statins lowered risk of cancer death and all cause mortality

Table 3

BMI/Weight loss

Study	Pubmed ID	Study Population (number of participants)	Follow up (years)	Levels of Body Mass Index compared	Breast cancer incidence RR (95% C.I.)	Overall Mortality RR (95% C.I.)	Summary
Eliassen et al.	16835425	49514 women	Up to 26 years	Gained 25 kg vs. weight maintenance post menopause	1.45 (1.27-1.66)	NA	Weight gain after menopause is associated with increased risk of breast cancer while weight loss is associated with lower risk of breast cancer compared to weight maintenance
				Gained 10 kg vs. weight maintenance post menopause	1.15 (1.03-1.35)		
				Lost weight vs. weight maintenance post menopause	0.45 (0.21-0.86)		
Hardefeldt et al	29223719	139 studies		Weight loss vs. no weight loss	0.82 (0.67-0.97)	NA	Weight loss is associated with reduced risk of breast cancer