Received: 22 January 2021 | Revised: 10 November 2021 | Accepted: 29 November 2021

DOI: 10.1002/oby.23369

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

REVIEW

Clinical Trials and Investigations

Obesity and breast cancer: Preventive and therapeutic possibilities for bariatric surgery

Trevor D. Crafts | Jennifer E. Tonneson | Bruce M. Wolfe | Andrea M. Stroud

Department of Surgery, Oregon Health & Science University, Portland, Oregon, USA

Correspondence
Andrea M. Stroud, Department of Surgery, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Mail Code: L223A, Portland, OR, 97239, USA.
Email: strouda@ohsu.edu

Abstract

Breast cancer is the most common and second deadliest malignancy in women. With rising obesity rates and building evidence for a strong association with obesity, the incidence of breast cancer can be expected to increase. Weight loss reduces breast cancer risk, the mechanisms of which are still poorly understood. As an effective therapy for obesity, bariatric surgery may be a powerful tool in breast cancer prevention and treatment. This review details the potential physiologic mechanisms that may underlie this association, as well as recently published studies that reinforce the link between bariatric surgery and a reduction in incident breast cancer. The use of bariatric surgery as an adjunct therapy in endometrial cancer also raises the potential for similar use in select breast cancer patients. Despite the expanding potential applications of bariatric surgery in this field, publications to date have been strictly observational, highlighting a need for future clinical trials.

INTRODUCTION

Breast cancer affects 1 in 8 women, making up 25.4% of all new cancer diagnoses in women (1). In the United States (US), breast cancer is the most common cancer diagnosed in females, after nonmelanoma skin cancer, and is the second leading cause of cancer-related death (2,3). An estimated 325,010 breast cancers were diagnosed in 2020, with 42,170 deaths attributable to breast cancer (2). Worldwide 2.3 million new cases of breast cancer were diagnosed in 2020, representing 11.7% of all cancer cases, making breast cancer the most commonly diagnosed cancer (4).

Obesity is a chronic, multifactorial disease, defined as abnormal or excessive accumulation of body fat resulting in decreased health and life-span (5). The prevalence of obesity continues to rise; in the US, an expected 50% of adults will have obesity, and 25% will have severe obesity by 2030 (6). Between 1975 to 2016, the global prevalence of obesity quadrupled for men (3% to 12%) and doubled for women (7% to 16%) (7). These alarming trends have no sign of abating, as the burden expands to additional populations, including rising rates of severe obesity in childhood and in low- and middle-income countries (7).

Numerous observational cohort studies have now linked obesity to an increased risk of multiple types of cancer (8,9). In their landmark study, Calle et al. found that obesity in the US contributed to 14% to 20% of all cancer deaths (8). Worldwide, it is estimated that 25% of all obesity-related cancers can be attributed to the increase in BMI between 1982 and 2002, whereas in the US, this number is a staggering 38% (10). The International Agency for Research on Cancer attributed "increased body fatness" to 14 different cancers, including breast (11). Obesity increases the risk of postmenopausal hormone receptor-positive breast cancer by 25% to 35% (12). Women with obesity are not only more likely to develop breast cancer, but they also are less likely to undergo screening and are diagnosed at a later stage (13,14). Unsurprisingly, women with obesity have worse overall- and breast-cancer-specific survival (15). Given the interconnected nature of these diseases, if the current pattern of population weight gain continues, breast cancer incidence and mortality will continue to rise. Innovative approaches to prevention, diagnosis, and treatment are needed for this growing, high-risk population.

Bariatric surgery has emerged as the current gold standard treatment for severe obesity. Bariatric surgery is also associated with a decreased risk of cancer incidence in populations with obesity,

although several studies have found this relationship was statistically significant only in women (16-21). Decreased breast cancer incidence is an important contributor to this risk reduction. Thus, in this review, we aim to clarify the relationship between obesity and breast cancer and explore the potential role of bariatric surgery in reducing this risk.

OBESITY AND BREAST CANCER

The association between obesity and elevated breast cancer risk is well established. The Million Women Study from the UK, for example, followed 1.2 million women aged 50 to 64 over a mean of 5.4 years and found that of the 45,037 breast cancers during that period, women with obesity had a nearly 30% higher risk of developing postmenopausal breast cancer (risk ratio [RR] 1.29, 95% CI: 1.22-1.36) than women without obesity (22). Similar results were seen in a meta-analysis of prospective studies assessing BMI and breast cancer risk, which showed women with BMI of 25, 30, and 35 kg/m^2 had relative risks of breast cancer of 1.02 (95% CI: 0.98-1.06), 1.12 (95% CI: 1.01-1.24), and 1.26 (95% CI: 1.07-1.50), respectively, as compared with women within the normal BMI range (23). This elevated risk is largely for postmenopausal hormone receptor-positive breast cancer. There are mixed results when looking at the link between obesity and premenopausal breast cancer, with one study showing a decreased risk of developing hormone receptor-positive breast cancer in these patients (24,25). Other studies suggest premenopausal women with obesity are at higher risk of developing triple-negative breast cancer (24,26).

Women with obesity also tend to present with more advanced disease and have worse breast-cancer-specific outcomes. In a secondary analysis of the Women's Health Initiative randomized clinical trials, BMI > 35 was strongly associated with risk for larger tumors (hazard ratio [HR] 2.12, 95% CI: 1.67-2.69, $p = 0.02$), locally advanced or distant disease (HR 1.94, 95% CI: 1.52-2.47, $p = 0.05$), death related to breast cancer (HR 2.25, 95% CI: 1.51-3.36, $p < 0.001$), and deaths after breast cancer (HR 2.11, 95% CI: 1.57-2.84, $p < 0.001$) (27). Similarly, a systematic review and meta-analysis of 82 studies showed worse disease-specific and overall survival for women with obesity. The study included 213,075 women with breast cancer and reported 41,477 deaths overall with 23,182 breast cancer deaths. The relative risk of all-cause mortality for women with BMI > 30 was 1.41 (95% CI: 1.29-1.53) and for breast-cancer-specific mortality was 1.35 (95% CI 1.24-1.47) compared with women with BMI 18.5 to 25.0 kg/m^2 (28). They also noted that regardless of when the weight was ascertained, for each 5-kg/m^2-increment increase in BMI, the risk of overall and breast-cancer-specific mortality increased (28). Risk of distant recurrence is also higher in women with obesity. In a large prospective cohort study from Denmark, for example, women with obesity had a 46% increased risk of distant recurrence after 5 to 10 years (HR 1.46, 95% CI: 1.11-1.92) (29).

Study Importance

What is already known?

- ► Women with obesity are at increased risk for postmenopausal estrogen receptor–positive breast cancer.
- ► Bariatric surgery has been associated with decreased breast cancer risk in observational studies.

What does this review add?

- ► This review highlights new publications linking bariatric surgery to decreased breast cancer incidence.
- ► The article discusses possible consequences of bariatric surgery on mammography and breast cancer screening.
- ► Bariatric surgery is proposed as a preventive and adjuvant therapy for breast cancer.

How might these results change the direction of research or the focus of clinical practice?

- ► Providers will be able to better understand the potential benefit of bariatric surgery for certain individuals, particularly those at high risk for breast cancer.
- ► We identify the need for a clearer understanding of the underlying mechanisms that impact breast cancer risk after weight loss and bariatric surgery.
- ► We call for a prospective clinical trial of bariatric surgery as a risk reduction strategy in breast cancer.

DISPARITIES IN OBESITY AND BREAST CANCER

Obesity disproportionately affects women, racial and ethnic minorities, and individuals of lower socioeconomic status (30). Obesity bias is highly prevalent both in the mainstream media and, unfortunately, among medical providers (31). Obesity bias contributes to individuals with obesity getting less routine medical care and cancer screening. Breast-cancer-specific outcomes in women with obesity are affected by a myriad of factors that may start as early as delays in diagnosis. A retrospective review of women aged 50 to 69 showed that noncompliance with screening mammography was higher in women with obesity, especially those with the highest BMI and Caucasian women (32). A meta-analysis of 16 studies also found that women age 40 and over with BMI > 25 were less likely to have had a mammogram in the preceding 2 years compared with women with normal weight (14).

Rates of obesity are highest among non-Hispanic Black women (33). Non-Hispanic Black women often have higher BMI and higher waist to hip ratios compared with Caucasian women, as well as elevated serum estrogen levels (31,34). Historically, rates of breast cancer were higher in Caucasian women, but as the rate of estrogen

receptor-positive (ER+) breast cancer increased, in large part because of increasing obesity prevalence, this increase was more rapid in non-Hispanic Black women. This led to a convergence in breast cancer rates between these two racial groups (35). The burden of obesity-related breast cancer is amplified in non-Hispanic Black women, who experience a 40% higher rate of breast cancer mortality (30,36). Even with earlier stage breast cancer, which is highly treatable, non-Hispanic Black women have more than a 30% higher risk of dying compared with their white counterparts (36). Although racial disparities in breast cancer are also multifactorial, one recent study found that this risk, in part, can be attributed to a higher prevalence of obesity and related comorbidities in non-Hispanic Black women (36).

MECHANISMS IMPLICATED IN OBESITY-ASSOCIATED BREAST CANCER

Multiple cell mediators and signaling pathways have been investigated in breast carcinogenesis. These mechanisms share a common theme of systemic metabolic, hormonal, and immune alterations producing a cellular microenvironment favorable to neoplasm development. Researchers have implicated chronic inflammation, adipokine signaling, metabolic dysregulation (hyperlipidemia, diabetes), microbiome dysbiosis, and, most notably, steroid sex-hormone mediators in obesity-associated breast carcinogenesis.

Steroid sex hormones

A strong connection has been established between sex hormones and postmenopausal breast cancer. Sex hormones are known to influence behavior of breast tumors, because of the expression of estrogen and progesterone receptors on the cell surface. Cumulative estrogen exposure is a key risk factor for breast cancer development, featured prominently in several risk prediction models (37).

Excess endogenous estrogen has been strongly implicated in the link between obesity and breast cancer. Adipose tissue is the primary extraglandular site of estrogen production as it contains aromatase, the rate-limiting enzyme in the conversion of androgen precursors to estrogens. The excess adiposity in individuals with obesity is associated with increased activity and abundance of this enzyme, promoting estrogen production (9). This may be particularly true after menopause, as estrogen production ceases in the ovaries and peripheral androgen conversion becomes the predominant source of endogenous estrogen (38). Estrogen levels are increased in postmenopausal women with obesity, primarily in the bioavailable forms of estradiol and estrone (39). Concurrently, sex hormone binding globulin (SHBG) is decreased, which contributes to increased bioavailability (39).

Within the adipose tissue of the breast, sites of increased aromatization have been histologically identified by clusters of dying adipocytes surrounded by macrophages. These entities, called crown-like structures, occur with higher frequency in women with obesity (40). These structures are associated with greater estrogen to androgen ratios both in tissues and systemically (40). It is thought that by altering local hormone levels, they contribute to pro-inflammatory and carcinogenic pathways.

Circulating systemic estrogens primarily interact with the estrogen receptor (ER) of breast cells. Induction of ER signaling causes proliferation and reduced apoptosis through multiple cell signaling pathways involved in tumorigenesis (21,41). Activation of mitochondrial genes and intracellular mediation of transcription factors are also influenced by the ER (41). Thus, estrogens induce not only the initiation but also the promotion and propagation of carcinogenesis. Furthermore, unstable quinone adducts are formed during estrogen metabolism, which cause direct depurination and oxidative damage to DNA (41).

Endogenous estrogen levels, particularly free estradiol, are associated with increased risk for postmenopausal breast cancer. Several studies have examined the mediating effect of estradiol on the risk of ER+ disease. The studies included women with BMI >25 who were postmenopausal and who had no prior exposure to hormone replacement therapy. Investigators have estimated estradiol accounts for 12% to 23.8% of the increased risk associated with obesity (42,43). The association between sex hormone levels and breast cancer has been reinforced by numerous studies demonstrating elevated relative risk in patients receiving exogenous hormone replacement therapy (41).

Other female sex hormones, such as progesterone and prolactin, likely have roles in breast carcinogenesis; however, their role is not as well characterized, especially as it relates to obesity. Progesterone increases proliferation of breast tissue. It stimulates ductal side branching and alveolar formation in mammary epithelium in conjunction with prolactin (44). The progesterone receptor modulates activity of the ER in models of breast cancer (45). Women who receive exogenous progestin compounds via hormone replacement therapy are at increased risk of breast cancer, even when compared with estrogen-only therapies (46). Androgens are also increased in postmenopausal women with obesity, notably free testosterone (39). Although elevated androgens are associated with increased breast cancer risk in postmenopausal women, the effect of obesity on this relationship has not yet been elucidated in the literature (37).

Anti-endocrine therapeutics have been developed to mitigate the pathologic effects of estrogen exposure in high-risk women. Chemoprevention with use of selective estrogen receptor modulators such as tamoxifen, as well as aromatase inhibitors (AIs) such as exemestane or anastrazole, has been shown to significantly reduce the risk of developing breast cancer in these high-risk women through randomized controlled trials (47). The effects of these medications in breast cancer risk reduction last well beyond the active treatment period (47,48). Of note, women with obesity can display resistance to AI medications (49). Aromatase resistance may itself be potentiated by hyperinsulinemia, as demonstrated in a rodent model (50).

Women who are breast cancer gene (BRCA) mutation carriers have a significantly higher lifetime risk of developing invasive breast cancer and they are consequentially offered estrogen-reducing procedures (47). Bilateral risk-reducing mastectomy and bilateral risk-reducing salpingo-oophorectomy can substantially reduce the risks of both breast and ovarian cancer (47,48). Studies on prophylactic bilateral risk-reducing salpingo-oophorectomy do not show a definite benefit in terms of breast cancer risk reduction for postmenopausal women; rather, it appears to be most beneficial for premenopausal women with BRCA2 mutations (48). It is possible that premenopausal women benefit most from this procedure as it affords the greatest reduction in cumulative estrogen exposure for them over time (48).

Insulin resistance, lipids, and metabolic syndrome

Insulin dysregulation is a hallmark of obesity-related metabolic changes. Epidemiologic evidence suggests that dysregulation of insulin and insulin resistance are linked to increased postmenopausal breast cancer risk. In one study, women with type 2 diabetes were found to have a 16% increased risk of breast cancer while controlling for BMI (51). In a meta-analysis of nine studies, "metabolic syndrome" was associated with a 52% increased risk of postmenopausal breast cancer (52). A later cohort study found that of all the elements of metabolic syndrome, elevated blood glucose was most strongly associated with increased risk of breast cancer in all women regardless of menopausal status (HR 1.47, 95% CI: 1.13-1.91) (53). Similar results were determined in an analysis of women in the Third National Health and Nutrition Examination Survey. Breast cancer mortality was increased in women with enlarged waist circumference (≥100.9 cm) (HR = 3.5, 95% CI: 1.14-10.51, p trend = 0.008) and elevated blood glucose (≥101 mg/dL) (HR = 3.2, 95% CI: 1.11-9.20, p trend = 0.03) (54). Women carrying a diagnosis of metabolic syndrome also have reduced disease-free and overall survival, as well as increased breast-cancer-specific mortality (54,55).

Insulin and the related insulinlike growth factor (IGF) protein family have both hormonal and mitogenic effects (56). Insulin is a powerful growth factor that stimulates protein synthesis, whereas IGF-1 inhibits apoptosis (56). Both have receptors in mammary tissue and promote sex hormone synthesis (57). Additionally, IGF-1 inhibits hepatic synthesis of SHBG, increasing the bioavailability of estrogen (37).

Hyperinsulinemia is thought to act pathologically on breast cancer cells. Insulin is known to generate cell proliferation in breast cancer cells *in vitro*, and insulin levels were positively associated with breast cancer risk in a large case-cohort study (57,58). High fasting insulin and C-peptide are associated with worse prognosis in early stage breast cancer (56,59). This association is stronger in women with type 2 diabetes and those with ER+ disease (59). However, mixed results have been found between IGF-1, its related binding proteins (IGFBP-1, IGFBP-3), and breast cancer (60-62). Krajcik et al. reported that IGF-1 and IGFBP-3 were associated with increased risk of breast cancer in premenopausal women (60). Schernhammer et al. found IGF-1 was associated with premenopausal risk, but not IGFBP-3 (62). However, a later study by Schernhammer et al. demonstrated no significant associations with premenopausal breast cancer (61). None of the IGF studies has demonstrated increased risks for postmenopausal patients. Interestingly, expression of the insulin receptor and activated IGF receptor is each independently associated with worse survival (63,64).

Lipid dysregulation has also been implicated in breast cancer risk, although results are mixed. High cholesterol is a risk factor for the onset of breast cancer and it is associated with poor prognosis (65). Interestingly, treatment with cholesterol-lowering medications is not associated with reduced breast cancer risk but it may be protective against breast cancer recurrence (65). A recent study using The Surveillance, Epidemiology, and End Results (SEER)-Medicare database reported that statin use improved breast-cancer-specific and overall survival in women with triple-negative breast cancer (66). At least two studies have demonstrated a correlation between high-density lipoprotein (HDL) and risk of breast cancer, but only one of them demonstrated the same with low-density lipoprotein (67,68). Using preoperative serum lipid profiles, Li et al. identified associations with breast cancer; low triglyceride was associated with worse disease-free survival and low levels of HDL with worse overall survival (69), although the design of this multivariate model was recently questioned (70). Further investigation is needed to better elucidate the possible association between serum lipids and breast cancer.

Chronic inflammation and adipokines

Adipose tissue is an active metabolic and endocrine organ, present in the breast as well as peripheral and visceral tissue. Adipose tissue exerts biological effects through its primary cell, the adipocyte (8). Obesity is thought to cause dysregulated adipocyte activity, which may promote inflammation as well tumorigenesis (71). Adipocytes have been shown with both *in vitro* and *in vivo* studies to induce proliferation, migration, and invasion of breast cancer cells (24,71-74).

Cellular mediators, known as adipokines, are secreted by adipocytes, and they include various growth factors, hormones, and cytokines (24,75). Adipokines can alter components of gene expression and apoptosis. Obesity increases certain adipokine levels, notably leptin, resistin, and visfatin. Leptin has been shown to have protumorigenic effects and it is associated with increased risk of breast cancer in multiple studies (76,77). Elevated resistin and visfatin levels also are associated with increased breast cancer risk and worse survival (78,79). Adiponectin, an adipokine that is downregulated in obesity, possesses insulin-sensitizing properties and has antiproliferative effects on breast epithelial cells (80). Adiponectin is inversely associated with breast cancer risk (80).

Adipokine mediation and cell signaling are affected by chronic inflammation secondary to obesity. Excess energy intake leads to adipocyte hypertrophy and hyperplasia, which cause mechanical stress

and relative hypoxia, resulting in an increased inflammatory milieu (81). Breast cancer patients with obesity have been shown to have raised levels of tumor necrosis factor-alpha (TNF-α), IL-6, and IL-1β, associated with worsened outcomes (24,82-84). TNF-α is correlated with stage of disease and lymph node metastases (84). Although IL-6 has several complex roles in the tumor microenvironment, systemic levels are thought to be reflective of tumor burden and to correlate with clinical disease stage, nodal metastases, and poor prognosis in these patients (82,84). Elevated IL-1β was found in 90% of invasive breast carcinomas, and levels were significantly higher when compared with ductal carcinoma in situ and benign lesions (83).

Microbiome dysbiosis

The human body is host to trillions of microbial cells, termed the microbiome, the vast majority of which reside in the gastrointestinal tract. With the introduction of advanced sequencing techniques scientists are increasingly able to characterize the human microbiome, which is implicated in disease, including cancer. Obesity is associated with an altered microbiome, with decreased microbial diversity and increased pathologic species, often termed "microbiome dysbiosis" (85). The obesity-associated changes in the gut microbiome are implicated in multiple cancers (86). The microbiome can fuel carcinogenesis by stimulating host cells to proliferate, disturbing apoptosis, modulating the immune response, and altering the metabolism of ingested nutrients (87).

There is evidence that breast cancer is associated with microbiome dysbiosis. Studies of the fecal microbiota of women with cancer compared with healthy controls have demonstrated altered composition and reduced diversity (88). One of the vital functions of the microbiome is to regulate the level of steroid hormones in the body, notably estrogen excretion and reabsorption via bacteria enzymatic activity. Deconjugation of estrogen and its metabolites by specific bacterial enzymes allows for increased resorption of estrogen via enterohepatic circulation (86). Flores et al. found that fecal microbiome richness was strongly correlated with systemic estrogens and that it could be attributed to specific microbial taxa (89). Thus, the altered microbiome composition seen with obesity may play a role in elevated systemic estrogen levels based on altered estrogen metabolism and resorption. The microbiome is a rapidly evolving field, which may prove to have both diagnostic and therapeutic implications.

WEIGHT LOSS AND BREAST CANCER RISK

The biological mechanisms associated with increased breast cancer risk in populations with obesity are potentially modifiable by weight loss. The association between weight change and breast cancer has been extensively reported in the literature. Obesity and weight gain in adulthood are associated with higher incidence of postmenopausal breast cancer (90). Studies of weight loss and overall cancer risk have had mixed results. In the Look AHEAD trial, the largest randomized trial of an intensive behavioral modification for weight loss in diabetes, after 8 years of follow-up, the intervention group lost 4.7%, and the usual care group lost 2.1% (91). A secondary analysis of this study found a trend toward decreased cancer risk, but the difference was not statistically significant (92). The lack of difference may reflect a small effect size as both groups lost weight, but the difference in weight loss was small.

Other epidemiologic cohort studies of weight loss have indeed reported decreased risk of breast cancer in postmenopausal women with decreased weight or with weight maintenance during adulthood (93,94). This benefit can be seen with even 5 lb of weight loss. The Pooling Project of Prospective Studies of Diet and Cancer (DCPP) evaluated survey data from 180,885 women with mean follow-up of 8.3 years. A linear relationship was found between weight loss and decreased breast cancer risk (>2 to 4.5 kg HR = 0.82, 95% CI: 0.70-0.96; >4.5 to <9 kg HR = 0.75, 95% CI: 0.63-0.90; ≥9 kg HR = 0.68, 95% CI: 0.50-0.93) (94). Of note, this study did not include a weight loss intervention.

In postmenopausal women with BMI >25 kg/m^2, weight loss is associated with changes in serum biomarkers that may reflect decreased cancer risk. Levels of estradiol, testosterone, insulin, C-reactive protein, and leptin are reduced, whereas serum adiponectin and SHBG are increased (95,96). Characterization of the metabolic and hormonal changes seen in patients with breast cancer and obesity may aid early detection strategies.

BARIATRIC SURGERY AND BREAST CANCER RISK

Multiple bariatric surgery cohorts have demonstrated a reduced risk of cancer compared with control groups with obesity (Table 1). In multiple studies, this effect has been statistically significant only in women. Of note, one of the most common cancers observed in these studies was breast cancer, and bariatric surgery has been associated with reduced breast cancer risk in several studies (17,21,97-102).

Christou et al. was one of the first studies to describe a reduced cancer risk after bariatric surgery (17). Breast cancer was the most common cancer and it was reduced in the post-bariatric surgery group by more than 80% compared with the control group (OR −0.17, 95% CI: 0.098-0.311, $p < 0.001$) (17). Schauer et al. conducted the largest cohort study of cancer risk and bariatric surgery, examining 22,198 surgical patients and 66,427 matched nonsurgical controls using multi-institutional data from the Kaiser Health system. They reported a 40% reduction in breast cancer in the bariatric surgical group compared with controls (HR 0.58, 95% CI: 0.44-0.77, $p < 0.001$) (18). Two studies using a national population-based cohort in the UK have found significant reductions in breast cancer risk among women who had bariatric surgery (97,100). Of note, two other important bariatric surgery studies examining cancer incidence have found a nonsignificant reduction in breast cancer. The Swedish Obese Subject Study

TABLE 1 Studies evaluating relationships between bariatric surgery and breast cancer

First author, year	Study design	Patients	Identification of control group	Mean age (y)	Mean BMI (kg/m^2)	Breast cancer risk[a]	Follow-up
Christou, 2008	Retrospective cohort	1,035 surgery 5,746 control	Provincial health insurance database	45.1 surgery 46.7 control	NA	RR 0.17, 95% CI: 0.098-0.311, $p < 0.001$	Up to maximum of 5 years
Adams, 2009	Retrospective cohort	6,709 surgery 9,609 control	Driver's license identification card applicants	38.9 surgery 39.1 control	44.9 surgery 47.4 control	HR 0.91, 95% CI: 0.67-1.24, $p = 0.54$	12.3 years for surgery 11.8 years for control
Sjöström, 2009[b]	Prospective, longitudinal cohort	1,420 surgery 1,447 control	Matched nonsurgical control	46.1 surgery 47.6 control	42.2 surgery 41.6 control	HR 0.71, 95% CI: 0.40-1.25, $p = 0.24$	10.9 years
Winder, 2017	Systematic review	10,533 surgery 20,130 control	8 studies included	40.9 surgery 43.2 control	Not reported as mean	OR 0.564, 95% CI: 0.453-0.702, $p < 0.001$	11.7 years
Arvani, 2018	Retrospective cohort, UK national population-based cohort	39,747 surgery 962,860 control	Hospital Episode Statistics database, *ICD-10* code for obesity	Not reported as mean	NA	SIR 0.76, 95% CI: 0.62-0.92	≤2 years, 32.8% surgery 41.8% control >2 years 67.2% surgery 58.2% control
Mackenzie, 2018	Retrospective cohort, UK national population-based database	8,794 surgery 8,794 control	Hospital Episode Statistics database, propensity-matched nonsurgical control	42 surgery 42 cotnrol	NA	OR 0.25, 95% CI: 0.19-0.33	55 months for surgery 55 months for control
Schauer, 2019	Retrospective observational cohort in Kaiser Health system	22,198 surgery 66,427 control	Electronic health record database, matched nonsurgical control	45.02 surgery 45.10 control	44.84 surgery 44.37 control	HR 0.58, 95% CI 0.44-0.77, $p < 0.001$	47 months for surgery 41 months for control
Feigelson, 2020	Retrospective observational cohort in Kaiser Health system, women only	17,998 surgery 53,889 control	Electronic health record database, matched nonsurgical control	44.6 surgery 44.7 control	44.6 surgery 44.1 control	HR 0.63, 95% CI: 0.52-0.76, $p < 0.001$	47.5 months for surgery 40.8 months for control
Tsui, 2020	Retrospective cohort, statewide database	55,781 surgery 247,102 control	Female patients with obesity and no history of bariatric surgery	43 surgery 44 control	NA	834 (1.50%) vs. 4,313 (1.75%), $p < 0.0001$	Database queried 2006-2012, cancer diagnosis up to 2016
Lovrics, 2021	Systematic review	105,294 surgery 1,001,645 control	11 included studies	43 surgery 49.7 control	44.8 surgery 44.6 control	RR 0.50, 95% CI: 0.37-0.67	4.7 years for surgery 2.7 years fir control

Abbreviations: HR, hazard ratio; *ICD-10*, *International Classification of Diseases*, Tenth *Revision;* NA, not available, OR, odds ratio; RR, risk ratio; SIR, standardized incidence ratio.

[a]Outcomes are reported as risk comparing surgical patients with nonsurgical control group.

[b]The Sjöström study reported results by gender; data in table limited to women. Cancer was not a predetermined end point of the study.

(SOS), the longest prospective, long-term study of bariatric surgery, unexpectedly found cancer was the most common cause of death, despite the fact that cancer was not a predefined end point. Breast cancer incidence was reduced in the post-bariatric group, but the result was not statistically significant (HR 0.75, 95% CI: 0.51-1.10) (103). In a retrospective cohort study of patients who underwent Roux-en-Y gastric bypass (RYGB) in Utah, breast cancer was the most commonly reported cancer, but there was not a statistically significant difference in incidence between the surgery and control group (16).

Tsui et al. recently published the incidence of female-specific (breast, endometrial, ovarian) cancers from the New York Statewide Planning and Research Cooperative System database (21). The surgical group consisted of 55,781 female bariatric surgery patients and it was matched with 247,102 nonsurgical controls. Incidence of breast cancer was lower in the surgical group (834 [1.50%] vs. 4,313 [1.75%], $p < 0.0001$). When stratified by operation, incidence after gastric band was 1.37%, RYGB 1.02%, and sleeve gastrectomy (SG) 0.82% ($p = 0.0003$) (21). An important limitation of this database study is the inability to determine menopausal status.

Systematic reviews and meta-analyses evaluating the risk of breast cancer after bariatric surgery have reported similar findings. Lovrics et al. pooled results from a total of 11 studies, including 1,106,939 patients, and found a 50% reduced risk of breast cancer following bariatric surgery (RR 0.50, 95% CI: 0.37-0.67) (104). Interestingly, the risk reduction was predominately in higher stage groups (III to IV), and bariatric surgery patients had higher risk of stage I disease (RR 1.23, 95% CI: 1.06-1.44), suggesting a tendency for diagnosis at an earlier stage in the surgical group (104). Earlier stage disease in the surgical group could suggest that women in bariatric surgery programs may receive more preventive health screening. The results were unchanged in several sensitivity analyses, including when controlling for age. In their systematic review, Winder et al. found bariatric surgery reduced the incidence of breast cancer by 44% including data from eight different studies (OR 0.564, 95% CI: 0.453-0.702) (105). However, the authors concluded that because of heterogeneity, their random effects model was more appropriate and did not reach statistical significance. A systematic review by Ishihara et al. of breast, ovarian, and endometrial cancers, which included seven studies, found that breast cancer risk was reduced by 49% in patients who had bariatric surgery (106).

In the case of premenopausal breast cancer, the effect of obesity is somewhat more controversial. Epidemiology studies suggest that obesity is associated with a reduced risk of premenopausal breast cancer (107,108). However, bariatric surgery cohorts challenge this theory. The Kaiser Health research team conducted a breast-cancer-specific analysis of their large, matched cohort (109). They identified 700 women with breast cancer, and those who had bariatric surgery had a 37% reduced risk compared with the nonsurgical group (HR 0.63, 95% CI: 0.52-0.76, $p < 0.001$). Interestingly, among both pre- and postmenopausal women, bariatric surgery was associated with a reduced risk of breast cancer. Premenopausal women had approximately a 30% reduced risk of breast cancer (HR 0.72, 95% CI: 0.54-0.94, $p = 0.02$), and postmenopausal women had a nearly 50% reduced breast cancer risk (HR 0.55, 95% CI: 0.42-0.72, $p < 0.001$). The risk reduction was even greater when only postmenopausal ER+ cases (HR 0.52, 95% CI: 0.39-0.70, $p < 0.001$) and premenopausal ER- cases (HR 0.36, 95% CI: 0.16-0.79, $p = 0.01$) were considered.

Male patients are notably absent in the literature on bariatric surgery in breast cancer. Although the pathophysiology of male breast cancer is less well understood, a sex hormone imbalance is thought to exist. Tumors in male patients are most often hormone receptor-positive (110). Bariatric surgery may be uniquely advantageous in this population. Male estrogen production is predominantly from the conversion of androgens by aromatase (111). Thus, reduction in adipose tissue after bariatric surgery may aid in reducing estrogen levels as is posited with postmenopausal breast cancer in females. Further investigation is warranted to determine the utility of bariatric surgery in male patients with increased risk for breast cancer, such as those who carry BRCA2 mutations. Also, surgical intervention may be preferable to therapies like tamoxifen and AIs, which have unfavorable adverse effects in male patients. AIs secondarily alter androgen levels, and tamoxifen is associated with decreased libido, erectile dysfunction, and cardiovascular disorders in male breast cancer patients (111).

Studies specifically evaluating breast cancer incidence after bariatric surgery have consistently demonstrated an association but not causation. Taken together though, these studies do satisfy several of Bradford Hill's criteria for causality, including biological plausibility, strength of association, temporality, and consistency across multiple studies. However, these studies have limitations. First, they are observational in nature, and most are retrospective. Studies using large databases may not include important clinical information, such as menopausal status or type of breast cancer. Finally, there may be selection bias, in which healthier patients are more often referred for bariatric surgery. The retrospective, observational nature of prior studies makes it difficult to elucidate the physiologic mechanisms underlying decreased breast cancer risk.

Discovering a possible causative effect for reduced breast cancer incidence after bariatric surgery requires additional research. To determine if there is an independent effect of surgery beyond weight loss, there is a need for prospective studies of breast cancer risk comparing women with obesity who undergo either bariatric surgery or medical weight management. It will be important to assess whether there is a threshold effect or dose–response relationship between breast cancer risk reduction and weight loss. Moreover, determining if different bariatric surgery procedures affect breast cancer risk independent of weight loss will be integral. Biological studies evaluating changes in serum sex hormones, hyperinsulinemia, inflammatory markers, and gut microbiome after bariatric surgery are needed to better understand how physiologic alterations induced by surgery might affect cancer risk. Animal models of bariatric surgery represent an untapped resource in the study of obesity-associated

cancer. Ultimately, for women with obesity at increased risk of breast cancer, development of a reliable noninvasive biomarker(s) would be paramount for early detection, comparing interventions, and measuring treatment effects.

BARIATRIC SURGERY AS AN ADJUNCT THERAPY IN BREAST CANCER

Aside from its potential for reducing the risk of incident breast cancer, bariatric surgery has been hypothesized to be a favorable adjuvant treatment modality. Obesity management is an important consideration in the adjuvant setting, given an association with higher rates of metastatic disease, recurrence, and mortality (15,112). There are several possible causes for these associations. First, women with obesity may present with more advanced disease, given that they are less likely to undergo mammographic screening (14). Second, women with obesity and ER+ tumors are also more likely to have a second primary breast cancer (113). Additionally, upregulation of obesity-related hormones may lead to a more biologically aggressive tumor. In one study, breast cancer patients with obesity were 46% more likely to develop distant metastases and 38% more likely to die of their disease (29). Finally, patients with obesity are more likely to be underdosed with traditional chemotherapy agents and be resistant to AI therapy (49,114). In some cases, they may be unable to receive chemotherapy in the first place because of preexisting comorbidities (15).

The favorable metabolic changes following bariatric surgery may conceivably enhance long-term outcomes. A recent retrospective study from Minnesota evaluated 13 patients who underwent laparoscopic RYGB or laparoscopic SG after being diagnosed with early stage (I/II) breast cancer (112). Median follow-up was 11.7 years following their cancer diagnosis and 5.3 years after bariatric surgery. Only 1 patient (7.7%) experienced a recurrence in this interval, which the authors note is lower than would be expected. The authors do note that the single recurrence happened within a month of bariatric surgery and was associated with a BRCA2 mutation, commenting that it is unlikely that weight loss would have been beneficial in this scenario. This study is limited by a small sample size, lack of advanced stage disease, and no comparator group. Nevertheless, it is suggestive of a possible therapeutic role for bariatric surgery in the adjuvant setting. How a possible risk reduction from surgery may compare with current adjuvant therapies is not yet known. Women receiving a selective estrogen receptor modulator in the adjuvant setting experience an estimated 31% reduction in mortality (115).

Bariatric surgery has already been explored as an adjunct for patients with endometrial cancer. Similar to breast cancer, there is a strong association between obesity and risk of endometrial carcinoma (116). Bariatric surgery has been shown to dramatically reduce the risk of the disease and also reverse atypical hyperplasia (117). Although it is unclear if bariatric surgery could have a similar benefit for premalignant lesions in breast cancer, this remains an intriguing hypothesis. Endometrial cancer is often diagnosed at an early stage and associated with favorable prognosis to such an extent that comorbidities drive survival. Thus, a recent case report details a robotic-assisted hysterectomy with concurrent laparoscopic RYGB in an effort to increase long-term survival (118). Another case report describes a young female with BMI 95 kg/m^2 who was diagnosed with endometrial cancer but was thought to be unsuitable for surgical management. Instead, she underwent laparoscopic SG with substantial resultant weight loss and was later able to successfully have her definitive cancer operation (119). Future investigations are warranted to determine if there should be analogous roles for bariatric procedures in breast cancer.

National quality and patient safety efforts have drastically improved safety and effectiveness of bariatric surgery. With less than 1% of eligible patients being referred for surgery, it is important to increase awareness of this effective therapy. Bariatric surgery has therapeutic potential, both as a prophylactic and adjuvant therapy, in women with obesity who are at higher risk for breast cancer development and worse breast cancer outcomes. Future research is needed to determine which patients would benefit most from bariatric surgery in the prevention and treatment of breast malignancy.

MAMMOGRAPHY IN BARIATRIC SURGERY PATIENTS

Women with obesity are known to be less likely to undergo breast cancer screening than women of normal weight (13,14). Being enrolled in a bariatric program may improve breast cancer screening, as preoperative age-appropriate cancer screening is recommended by the American Society for Metabolic and Bariatric Surgery (120). By identifying previously undetected lesions or even initiating surveillance for radiographically suspicious lesions, women have an opportunity for earlier recognition and treatment.

As many bariatric surgery practitioners encourage breast cancer screening for their patients preoperatively, selection bias may be introduced when evaluating the protective effect of these procedures on breast cancer risk. Patients who have a breast cancer detected during preoperative screening may then not undergo bariatric surgery, leading observational studies to detect fewer breast cancers in surgery groups. However, certain evidence offsets this bias. First, there is room for improvement in preoperative screening policies. In response to a survey of preoperative screening practices, 49% of surgeons (n = 274) did not require mammograms prior to surgery (121). Second, society guidelines for preoperative screening mammography have been more recent (2020), and these historic cohorts are unlikely to have been impacted by such practices, as practice patterns assuredly lag behind policy (120). These observations underscore the need for prospective studies that control for screening practices.

The effects of bariatric surgery and weight loss on the efficacy of mammograms is less clear. Increased breast density decreases the sensitivity of mammography, reducing neoplasm detection (122). Obesity and breast density are both independent risk factors for

breast cancer; however, obesity is inversely related to breast density (123). Following the weight loss seen in bariatric surgery, the decrease in breast adipose volume has been shown to be more substantial than that of fibroglandular volume, leading to an overall increase in volumetric breast density (98). Despite this quantitative difference, there was no difference in Breast Imaging Reporting and Data System score before and after bariatric surgery. Potential increases in breast density would be thought to confer a paradoxically greater risk of breast cancer for bariatric surgery patients. However, the authors comment that absolute decreases in fibroglandular volume may be responsible for risk reduction after weight loss, as proliferation of glandular tissue is hormonally mediated and breast cancer is a neoplastic process of the mammary glands rather than adipose tissue.

CONCLUSION

The incidence of obesity is increasing both in the US and globally. Breast cancer is the most frequently diagnosed cancer, and obesity is a well-established risk factor. As the public health burden of obesity grows, strategies to mitigate the risk and alleviate the consequences of breast cancer are imperative. Bariatric surgery is an efficacious weight loss treatment and it has been associated with decreased risk of breast cancer in several recent studies. The underlying mechanism of reduced breast cancer risk after bariatric surgery remains an unanswered question. Ideally, future treatment of obesity would focus on individual risk profiles and expected response to treatment. Bariatric surgery as a risk mitigation strategy in women at high risk for breast cancer and surgical weight loss to improve survivorship in women with obesity and breast cancer are important research targets. Future investigations are needed to better elucidate the role for bariatric surgery in the prevention and treatment of breast cancer.O

CONFLICT OF INTEREST

AMS is the recipient of the Collins Medical Trust award, but this was not used for the preparation of this manuscript. The other authors declared no conflict of interest.

ORCID

Trevor D. Crafts https://orcid.org/0000-0002-5860-8014
Bruce M. Wolfe https://orcid.org/0000-0002-3373-1198

REFERENCES

1. World Cancer Research Fund. Worldwide cancer data. https://www.wcrf.org/dietandcancer/worldwide-cancer-data/
2. American Cancer Society. *Cancer Facts & Figures 2020*. American Cancer Society; 2020.
3. Centers for Disease Control and Prevention. Breast cancer statistics. Updated June 8, 2021. https://www.cdc.gov/cancer/breast/statistics/index.htm
4. World Health Organization. Breast cancer now most common form of cancer: WHO taking action. Published February 3, 2021. https://www.who.int/news/item/03-02-2021-breast-cancer-now-most-common-form-of-cancer-who-taking-action
5. World Health Organization. Overweight and obesity. Updated June 9, 2021.
6. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. *N Engl J Med*. 2019;381:2440-2450.
7. Sung H, Siegel RL, Torre LA, et al. Global patterns in excess body weight and the associated cancer burden. *CA Cancer J Clin*. 2019;69:88-112.
8. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348:1625-1638.
9. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371:569-578.
10. Arnold M, Pandeya N, Byrnes G, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. *Lancet Oncol*. 2015;16:36-46.
11. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer-viewpoint of the IARC Working Group. *N Engl J Med*. 2016;375:794-798.
12. Jiralerspong S, Goodwin PJ. Obesity and breast cancer prognosis: evidence, challenges, and opportunities. *J Clin Oncol*. 2016;34:4203-4216.
13. Lee K, Kruper L, Dieli-Conwright CM, Mortimer JE. The impact of obesity on breast cancer diagnosis and treatment. *Curr Oncol Rep*. 2019;21:41. doi:10.1007/s11912-019-0787-1
14. Maruthur NM, Bolen S, Brancati FL, Clark JM. Obesity and mammography: a systematic review and meta-analysis. *J Gen Intern Med*. 2009;24:665-677.
15. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. *Breast Cancer Res Treat*. 2010;123:627-635.
16. Adams TD, Stroup AM, Gress RE, et al. Cancer incidence and mortality after gastric bypass surgery. *Obesity (Silver Spring)*. 2009;17:796-802.
17. Christou NV, Lieberman M, Sampalis F, Sampalis JS. Bariatric surgery reduces cancer risk in morbidly obese patients. *Surg Obes Relat Dis*. 2008;4:691-695.
18. Schauer DP, Feigelson HS, Koebnick C, et al. Bariatric surgery and the risk of cancer in a large multisite cohort. *Ann Surg*. 2019;269:95-101.
19. Sjöström L, Gummesson A, Sjöström CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncol*. 2009;10:653-662.
20. Sjöström L, Narbro K, Sjöström CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med*. 2007;357:741-752.
21. Tsui ST, Yang J, Zhang X, et al. The risk of female-specific cancer after bariatric surgery in the state of New York. *Surg Endosc*. 2021;35:4267-4274.
22. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*. 2007;335:1134. doi:10.1136/bmj.39367.495995.AE
23. Xia X, Chen W, Li J, et al. Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. *Sci Rep*. 2014;4:7480. doi:10.1038/srep07480
24. Kolb R, Zhang W. Obesity and breast cancer: a case of inflamed adipose tissue. *Cancers (Basel)*. 2020;12:1686. doi:10.3390/cancers12061686
25. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and

progesterone receptor status–a meta-analysis. *Int J Cancer*. 2009;124:698-712.
26. Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2013;137:307-314.
27. Neuhouser ML, Aragaki AK, Prentice RL, et al. Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the women's health initiative randomized clinical trials. *JAMA Oncol*. 2015;1:611-621.
28. Chan D, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol*. 2014;25:1901-1914.
29. Ewertz M, Jensen M-B, Gunnarsdóttir KÁ, et al. Effect of obesity on prognosis after early-stage breast cancer. *J Clin Oncol*. 2011;29:25-31.
30. Yedjou CG, Sims JN, Miele L, et al. Health and racial disparity in breast cancer. *Adv Exp Med Biol*. 2019;1152:31-49.
31. Puhl RM, Heuer CA. Obesity stigma: important considerations for public health. *Am J Public Health*. 2010;100:1019-1028.
32. Lee Y, Doumouras AG, Yu J, et al. Complete resolution of nonalcoholic fatty liver disease after bariatric surgery: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2019;17:1040-1060 e11.
33. National Institute for Diabetes and Digestive and Kidney Diseases. Overweight and obesity statistics. Updated September 2021. https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity
34. Lamon-Fava S, Barnett JB, Woods MN, et al. Differences in serum sex hormone and plasma lipid levels in Caucasian and African-American premenopausal women. *J Clin Endocrinol Metab*. 2005;90:4516-4520.
35. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer statistics, 2015: convergence of incidence rates between black and white women. *CA Cancer J Clin*. 2016;66:31-42.
36. Nyrop KA, Damone EM, Deal AM, et al. Obesity, comorbidities, and treatment selection in Black and White women with early breast cancer. *Cancer*. 2021;127:922–930.
37. Baglietto L, Severi G, English DR, et al. Circulating steroid hormone levels and risk of breast cancer for postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2010;19:492-502.
38. Susan G. Komen. Body weight and weight gain. Updated March 1, 2021. https://www.komen.org/breast-cancer/risk-factor/weight/
39. Liedtke S, Schmidt ME, Vrieling A, et al. Postmenopausal sex hormones in relation to body fat distribution. *Obesity (Silver Spring)*. 2012;20:1088-1095.
40. Mullooly M, Yang HP, Falk RT, et al. Relationship between crown-like structures and sex-steroid hormones in breast adipose tissue and serum among postmenopausal breast cancer patients. *Breast Cancer Res*. 2017;19:8. doi:10.1186/s13058-016-0791-4
41. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. *N Engl J Med*. 2006;354:270-282.
42. Hvidtfeldt UA, Gunter MJ, Lange T, et al. Quantifying mediating effects of endogenous estrogen and insulin in the relation between obesity, alcohol consumption, and breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2012;21:1203-1212.
43. Schairer C, Fuhrman BJ, Boyd-Morin J, et al. Quantifying the role of circulating unconjugated estradiol in mediating the body mass index-breast cancer association. *Cancer Epidemiol Biomarkers Prev*. 2016;25:105-113.
44. Atwood CS, Hovey RC, Glover JP, et al. Progesterone induces side-branching of the ductal epithelium in the mammary glands of peripubertal mice. *J Endocrinol*. 2000;167:39-52.
45. Mohammed H, Russell IA, Stark R, et al. Corrigendum: progesterone receptor modulates Erα action in breast cancer. *Nature*. 2015;526:144. doi:10.1038/nature14959
46. Asi N, Mohammed K, Haydour Q, et al. Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. *Syst Rev*. 2016;5:121. doi:10.1186/s13643-016-0294-5
47. Pruthi S, Heisey RE, Bevers TB. Chemoprevention for breast cancer. *Ann Surg Oncol*. 2015;22:3230-3235.
48. Thorat MA, Balasubramanian R. Breast cancer prevention in high-risk women. *Best Pract Res Clin Obstet Gynaecol*. 2020;65:18-31.
49. Gnant M, Pfeiler G, Stöger H, et al. The predictive impact of body mass index on the efficacy of extended adjuvant endocrine treatment with anastrozole in postmenopausal patients with breast cancer: an analysis of the randomised ABCSG-6a trial. *Br J Cancer*. 2013;109:589-596.
50. Schech A, Yu S, Goloubeva O, McLenithan J, Sabnis G. A nude mouse model of obesity to study the mechanisms of resistance to aromatase inhibitors. *Endocr Relat Cancer*. 2015;22:645-656.
51. Boyle P, Boniol M, Koechlin A, et al. Diabetes and breast cancer risk: a meta-analysis. *Br J Cancer*. 2012;107:1608-1617.
52. Esposito K, Chiodini P, Capuano A, et al. Metabolic syndrome and postmenopausal breast cancer: systematic review and meta-analysis. *Menopause*. 2013;20:1301-1309.
53. Agnoli C, Grioni S, Sieri S, et al. Metabolic syndrome and breast cancer risk: a case-cohort study nested in a multicentre andomi cohort. *PLoS One*. 2015;10:e0128891. doi:10.1371/journal.pone.0128891
54. Gathirua-Mwangi WG, Song Y, Monahan PO, Champion VL, Zollinger TW. Associations of metabolic syndrome and C-reactive protein with mortality from total cancer, obesity-linked cancers and breast cancer among women in NHANES III. *Int J Cancer*. 2018;143:535-542.
55. Buono G, Crispo A, Giuliano M, et al. Metabolic syndrome and early stage breast cancer outcome: results from a prospective observational study. *Breast Cancer Res Treat*. 2020;182:401-409.
56. Goodwin PJ, Ennis M, Pritchard KI, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol*. 2002;20:42-51.
57. Gunter MJ, Hoover DR, Yu H, et al. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst*. 2009;101:48-60.
58. Chappell J, Leitner JW, Solomon S, Golovchenko I, Goalstone ML, Draznin B. Effect of insulin on cell cycle progression in MCF-7 breast cancer cells. Direct and potentiating influence. *J Biol Chem*. 2001;276:38023-38028.
59. Irwin ML, Duggan C, Wang C-Y, et al. Fasting C-peptide levels and death resulting from all causes and breast cancer: the health, eating, activity, and lifestyle study. *J Clin Oncol*. 2011;29:47-53.
60. Krajcik RA, Borofsky ND, Massardo S, Orentreich N. Insulin-like growth factor I (IGF-I), IGF-binding proteins, and breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2002;11:1566-1573.
61. Schernhammer ES, Holly JM, Hunter DJ, Pollak MN, Hankinson SE. Insulin-like growth factor-I, its binding proteins (IGFBP-1 and IGFBP-3), and growth hormone and breast cancer risk in The Nurses Health Study II. *Endocr Relat Cancer*. 2006;13:583-592.
62. Schernhammer ES, Holly JM, Pollak MN, Hankinson SE. Circulating levels of insulin-like growth factors, their binding proteins, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2005;14:699-704.
63. Goodwin PJ, Ennis M, Pritchard KI, et al. Insulin- and obesity-related variables in early-stage breast cancer: correlations and time course of prognostic associations. *J Clin Oncol*. 2012;30:164-171.
64. Law JH, Habibi G, Hu K, et al. Phosphorylated insulin-like growth factor-i/insulin receptor is present in all breast cancer subtypes and is related to poor survival. *Cancer Res*. 2008;68:10238-10246.
65. Nelson ER. The significance of cholesterol and its metabolite, 27-hydroxycholesterol in breast cancer. *Mol Cell Endocrinol*. 2018;466:73-80.

66. Nowakowska MK, Lei X, Thompson MT, et al. Association of statin use with clinical outcomes in patients with triple-negative breast cancer. *Cancer*. 2021;127:4142-4150.
67. Beeghly-Fadiel A, Khankari NK, Delahanty RJ, et al. A Mendelian randomization analysis of circulating lipid traits and breast cancer risk. *Int J Epidemiol*. 2020;49:1117-1131.
68. Johnson KE, Siewert KM, Klarin D, et al. The relationship between circulating lipids and breast cancer risk: a Mendelian randomization study. *PLoS Medicine*. 2020;17:e1003302. doi:10.1371/journal.pmed.1003302
69. Li X, Tang H, Wang J, et al. The effect of preoperative serum triglycerides and high-density lipoprotein-cholesterol levels on the prognosis of breast cancer. *Breast*. 2017;32:1-6.
70. Pakzad R, Safiri S. The effect of preoperative serum triglycerides and high-density lipoprotein-cholesterol levels on the prognosis of breast cancer: methodological issue. *Breast*. 2017;36:103-104.
71. Chu DT, Phuong TNT, Tien NLB, et al. The effects of adipocytes on the regulation of breast cancer in the tumor microenvironment: an update. *Cells*. 2019;8:857. doi:10.3390/cells8080857
72. Dirat B, Bochet L, Dabek M, et al. Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. *Cancer Res*. 2011;71:2455-2465.
73. Lee Y, Jung WH, Koo JS. Adipocytes can induce epithelial-mesenchymal transition in breast cancer cells. *Breast Cancer Res Treat*. 2015;153:323-335.
74. Wu Q, Li B, Li Z, Li J, Sun S, Sun S. Cancer-associated adipocytes: key players in breast cancer progression. *J Hematol Oncol*. 2019;12:95. doi:10.1186/s13045-019-0778-6
75. Ailhaud G. Adipose tissue as a secretory organ: from adipogenesis to the metabolic syndrome. *C R Biol*. 2006;329:570-577; discussion 653–5.
76. Gu L, Wang CD, Cao C, Cai LR, Li DH, Zheng YZ. Association of serum leptin with breast cancer: a meta-analysis. *Medicine (Baltimore)*. 2019;98:e14094. doi:10.1097/MD.0000000000014094
77. Stroud AM, Dewey EN, Husain FA, et al. Association between weight loss and serum biomarkers with risk of incident cancer in the Longitudinal Assessment of Bariatric Surgery cohort. *Surg Obes Relat Dis*. 2020;16:1086-1094.
78. Dalamaga M, Sotiropoulos G, Karmaniolas K, Pelekanos N, Papadavid E, Lekka A. Serum resistin: a biomarker of breast cancer in postmenopausal women? Association with clinicopathological characteristics, tumor markers, inflammatory and metabolic parameters. *Clin Biochem*. 2013;46:584-590.
79. Lee YC, Yang YH, Su JH, Chang HL, Hou MF, Yuan SS. High visfatin expression in breast cancer tissue is associated with poor survival. *Cancer Epidemiol Biomarkers Prev*. 2011;20:1892-1901.
80. Gunter MJ, Wang T, Cushman M, et al. Circulating adipokines and inflammatory markers and postmenopausal breast cancer risk. *J Natl Cancer Inst*. 2015;107:djv169. doi:10.1093/jnci/djv169
81. Trayhurn P. Hypoxia and adipose tissue function and dysfunction in obesity. *Physiol Rev*. 2013;93:1-21.
82. Dethlefsen C, Hojfeldt G, Hojman P. The role of intratumoral and systemic IL-6 in breast cancer. *Breast Cancer Res Treat*. 2013;138:657-664.
83. Jin L, Yuan RQ, Fuchs A, et al. Expression of interleukin-1beta in human breast carcinoma. *Cancer*. 1997;80:421-434.
84. Ma Y, Ren Y, Dai ZJ, Wu CJ, Ji YH, Xu J. IL-6, IL-8 and TNF-alpha levels correlate with disease stage in breast cancer patients. *Adv Clin Exp Med*. 2017;26:421-426.
85. Liu BN, Liu XT, Liang ZH, Wang JH. Gut microbiota in obesity. *World J Gastroenterol*. 2021;27:3837-3850.
86. Plottel CS, Blaser MJ. Microbiome and malignancy. *Cell Host Microbe*. 2011;10:324-335.
87. Parida S, Sharma D. The microbiome-estrogen connection and breast cancer risk. *Cells*. 2019;8:1642. doi:10.3390/cells8121642
88. Goedert JJ, Jones G, Hua X, et al. Investigation of the association between the fecal microbiota and breast cancer in postmenopausal women: a population-based case-control pilot study. *J Natl Cancer Inst*. 2015;107:djv147. doi:10.1093/jnci/djv147
89. Flores R, Shi J, Fuhrman B, et al. Fecal microbial determinants of fecal and systemic estrogens and estrogen metabolites: a cross-sectional study. *J Transl Med*. 2012;10:253. doi:10.1186/1479-5876-10-253
90. Keum NaNa, Greenwood DC, Lee DH, et al. Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. *J Natl Cancer Inst*. 2015;107:djv088. doi:10.1093/jnci/djv088
91. Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. *Obesity (Silver Spring)*. 2014;22:5-13.
92. Look AHEAD Research Group; Yeh H-C, Bantle JP, Cassidy-Begay M, et al. Intensive weight loss intervention and cancer risk in adults with type 2 diabetes: analysis of the Look AHEAD Randomized Clinical Trial. *Obesity (Silver Spring)*. 2020;28:1678-1686.
93. Chlebowski RT, Luo J, Anderson GL, et al. Weight loss and breast cancer incidence in postmenopausal women. *Cancer*. 2019;125:205-212.
94. Teras LR, Patel AV, Wang M, et al. Sustained weight loss and risk of breast cancer in women 50 years and older: a pooled analysis of prospective data. *J Natl Cancer Inst*. 2020;112:929-937.
95. de Roon M, May AM, McTiernan A, et al. Effect of exercise and/or reduced calorie dietary interventions on breast cancer-related endogenous sex hormones in healthy postmenopausal women. *Breast Cancer Res*. 2018;20:81. doi:10.1186/s13058-018-1009-8
96. Fabian CJ, Kimler BF, Donnelly JE, et al. Favorable modulation of benign breast tissue and serum risk biomarkers is associated with > 10 % weight loss in postmenopausal women. *Breast Cancer Res Treat*. 2013;142:119-132.
97. Aravani A, Downing A, Thomas JD, Lagergren J, Morris EJA, Hull MA. Obesity surgery and risk of colorectal and other obesity-related cancers: an English population-based cohort study. *Cancer Epidemiol*. 2018;53:99-104.
98. Hassinger TE, Mehaffey JH, Knisely AT, et al. The impact of bariatric surgery on qualitative and quantitative breast density. *Breast J*. 2019;25:1198-1205.
99. Heshmati K, Harris DA, Rosner B, et al. Association of bariatric surgery status with reduced HER2+ breast cancers: a retrospective cohort study. *Obes Surg*. 2019;29:1092-1098.
100. Mackenzie H, Markar SR, Askari A, et al. Obesity surgery and risk of cancer. *Br J Surg*. 2018;105:1650-1657.
101. Tao W, Santoni G, von Euler-Chelpin MY, et al. Cancer risk after bariatric surgery in a cohort study from the five Nordic countries. *Obes Surg*. 2020;30:3761-3767.
102. Tsui ST, Yang J, Zhang X, et al. Development of cancer after bariatric surgery. *Surg Obes Relat Dis*. 2020;16:1586-1595.
103. Anveden Å, Taube M, Peltonen M, et al. Long-term incidence of female-specific cancer after bariatric surgery or usual care in the Swedish Obese Subjects Study. *Gynecol Oncol*. 2017;145:224-229.
104. Lovrics O, Butt J, Lee Y, et al. The effect of bariatric surgery on breast cancer incidence and characteristics: a meta-analysis and systematic review. *Am J Surg*. 2021;222:715-722.
105. Winder AA, Kularatna M, MacCormick AD. Does bariatric surgery affect the incidence of breast cancer development? A systematic review. *Obes Surg*. 2017;27:3014-3020.
106. Ishihara BP, Farah D, Fonseca MCM, Nazario A. The risk of developing breast, ovarian, and endometrial cancer in obese women submitted to bariatric surgery: a meta-analysis. *Surg Obes Relat Dis*. 2020;16:1596-1602.

107. García-Estévez L, Cortés J, Pérez S, Calvo I, Gallegos I, Moreno-Bueno G. Obesity and breast cancer: a paradoxical and controversial relationship influenced by menopausal status. *Front Oncol*. 2021;11:705911. doi:10.3389/fonc.2021.705911
108. Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. *Epidemiol Rev*. 2014;36:114-136.
109. Feigelson HS, Caan B, Weinmann S, et al. Bariatric surgery is associated with reduced risk of breast cancer in both premenopausal and postmenopausal women. *Ann Surg*. 2020;272:1053-1059.
110. Hayes TG. Pharmacologic treatment of male breast cancer. *Expert Opin Pharmacother*. 2009;10:2499-2510.
111. de Ronde W, de Jong FH. Aromatase inhibitors in men: effects and therapeutic options. *Reprod Biol Endocrinol*. 2011;9:93. doi:10.1186/1477-7827-9-93
112. Zhang S, Ikramuddin S, Beckwith HC, Sheka AC, Wirth KM, Blaes AH. The impact of bariatric surgery on breast cancer recurrence: case series and review of literature. *Obes Surg*. 2020;30:780-785.
113. Li CI, Daling JR, Porter PL, Tang MT, Malone KE. Relationship between potentially modifiable lifestyle factors and risk of second primary contralateral breast cancer among women diagnosed with estrogen receptor-positive invasive breast cancer. *J Clin Oncol*. 2009;27:5312-5318.
114. Griggs JJ, Sorbero ME, Lyman GH. Undertreatment of obese women receiving breast cancer chemotherapy. *Arch Intern Med*. 2005;165:1267-1273.
115. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365:1687-1717.
116. Shaw E, Farris M, McNeil J, Friedenreich C. Obesity and endometrial cancer. *Recent Results Cancer Res*. 2016;208:107-136.
117. Upala S, Anawin S. Bariatric surgery and risk of postoperative endometrial cancer: a systematic review and meta-analysis. *Surg Obes Relat Dis*. 2015;11:949-955.
118. Shafa A, Kumar A, Torres D, McKenzie TJ. Minimally invasive hysterectomy and bariatric surgery to improve endometrial cancer survivorship. *Obstet Gynecol*. 2019;134:570-572.
119. Montemorano L, Smrz SA, Jalilvand AD, Noria SF, Salani R. Bariatric surgery after failed conservative management in a morbidly obese patient with endometrial cancer. *Gynecol Oncol Rep*. 2019;27:69-71.
120. Ghiassi S, El Chaar M, Aleassa EM, et al. ASMBS position statement on the relationship between obesity and cancer, and the role of bariatric surgery: risk, timing of treatment, effects on disease biology, and qualification for surgery. *Surg Obes Relat Dis*. 2020;16:713-724.
121. Winfree LE, Henretta MS, Hallowell PT, Modesitt SC. Preoperative gynecologic evaluation of bariatric surgery patients: improving cancer detection in a high-risk population. *J Am Coll Surg*. 2010;211:256-262.
122. Winkler NS, Raza S, Mackesy M, Birdwell RL. Breast density: clinical implications and assessment methods. *Radiographics*. 2015;35:316-324.
123. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density and breast cancer risk: current understanding and future prospects. *Breast Cancer Res*. 2011;13:223. doi:10.1186/bcr2942

How to cite this article: Crafts TD, Tonneson JE, Wolfe BM, Stroud AM. Obesity and breast cancer: Preventive and therapeutic possibilities for bariatric surgery. *Obesity (Silver Spring)*. 2022;30:587–598. doi:10.1002/oby.23369