



# Overall and Estrogen Receptor–Positive Breast Cancer Incidences Are Decreased Following Bariatric Surgery

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## Abstract

**Introduction** Bariatric surgery treats morbid obesity resulting in long-lasting weight loss. Elevated body mass index (BMI) increases breast cancer risk. We hypothesized that patients undergoing bariatric surgery would have decreased overall and estrogen receptor (ER)-positive breast cancer incidences compared to a propensity-matched non-surgical cohort.

**Methods** The bariatric population included all female patients who underwent weight loss surgery at a single institution from 1985 to 2015. Patients from all outpatient visits were propensity score matched 1:1 with bariatric patients using BMI, comorbidities, demographics, and insurance status. The primary outcome was breast cancer incidence. Univariate analyses compared the groups.

**Results** A total of 4860 patients were included, with 2430 in both groups. Median follow-up time from date of surgery or morbid obesity diagnosis was 5.7 years. There were no differences in age or comorbidities aside from gastroesophageal reflux disease. Seventeen (0.7%) patients in the surgery group were subsequently diagnosed with breast cancer versus 32 (1.3%) in the non-surgery group ( $p = 0.03$ ). The non-surgery group had more ER-positive tumors [4 (36.4%) vs. 22 (71.0%);  $p = 0.04$ ].

**Conclusion** Female patients who underwent bariatric surgery were less frequently diagnosed with any breast cancer and ER-positive breast cancer versus a propensity-matched cohort suggesting a possible oncologic benefit to weight loss surgery.

**Keywords** Morbid obesity · Weight loss surgery · Cancer risk

## Introduction

The overall prevalence of obesity among adults continues to rise. In the USA alone, nearly one third of the adult population is obese with a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> [1, 2]. Obesity is associated with a wide range of comorbidities, such as diabetes mellitus and cardiovascular disease, resulting in increased morbidity and mortality compared to non-obese adults [3, 4].

The risk of malignancy, including colon, pancreatic, endometrial, and breast cancer, is increased in obese individuals. Additionally, obesity is associated with worsened cancer

survival [4–6]. For breast cancer specifically, BMI is linked to an increased risk of locally advanced disease at the time of diagnosis, recurrence, and mortality [7, 8]. As breast cancer remains the most commonly diagnosed cancer among women in the USA, the impact of obesity on its incidence and mortality is consequential [6, 9].

Bariatric surgery has been consistently shown to be more efficacious than medical management alone in achieving substantial weight loss and comorbidity amelioration in obese patients [10–12]. Lasting improvements in diabetes mellitus and metabolic syndrome—two known risk factors for cancer development—are also achieved with weight loss surgery [3, 12]. Cancer-related mortality is also positively impacted [13, 14]. Several observational studies have additionally shown a decrease in overall cancer incidence following bariatric surgery, particularly in women, though there is limited data available on specific cancer types [15–17]. This study aimed to further assess the impact of bariatric surgery in an obese patient population on overall and molecular subtype-specific breast cancer incidence as compared to a propensity-matched non-surgical obese cohort.

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## Materials and Methods

### Patients

The Institutional Review Board (#17132) approved this study with waiver of consent due to its retrospective nature. All adult female patients who underwent bariatric surgery (including Roux-en-Y gastric bypass, sleeve gastrectomy, and adjustable gastric banding) for morbid obesity at a single academic institution between 1985 and 2015 were retrospectively identified from a prospectively maintained database [11]. To identify an appropriate control group, an institutional clinical data repository (CDR) of all routine outpatient visits was queried to identify a non-surgical cohort of 27,345 morbidly obese female patients who did not undergo weight loss surgery. Patients with a history of breast cancer preexisting either date of surgery (surgical group) or date of morbid obesity diagnosis (non-surgical group) were excluded prior to the propensity match. Propensity-matched groups were then generated to facilitate adjusted comparisons between the surgical and non-surgical cohorts.

### Data Collection

Patient demographics, BMI, relevant comorbidities (diabetes mellitus, hypertension, gastroesophageal reflux disease, current smoking status, congestive heart failure/coronary artery disease), and insurance status were captured through the CDR for all patients. These baseline characteristics were collected at the time of initial diagnosis of morbid obesity ( $\text{BMI} \geq 35 \text{ kg/m}^2$ ) for non-surgical control patients and at the time of the preoperative appointment for the patients undergoing bariatric surgery. Breast cancer diagnoses were identified through the CDR for both surgical and non-surgical patients. For all patients with a breast cancer diagnosis, review of the electric medical record was undertaken to identify tumor characteristics. This data is incomplete for

some patients that had their cancers treated at outside institutions with incomplete pathological records available for our review. Patients included in the analysis contributed time up until the date of last available follow-up; thus, a diagnosis of breast cancer was captured only if it occurred during the included time for each individual patient.

### Statistical Analyses

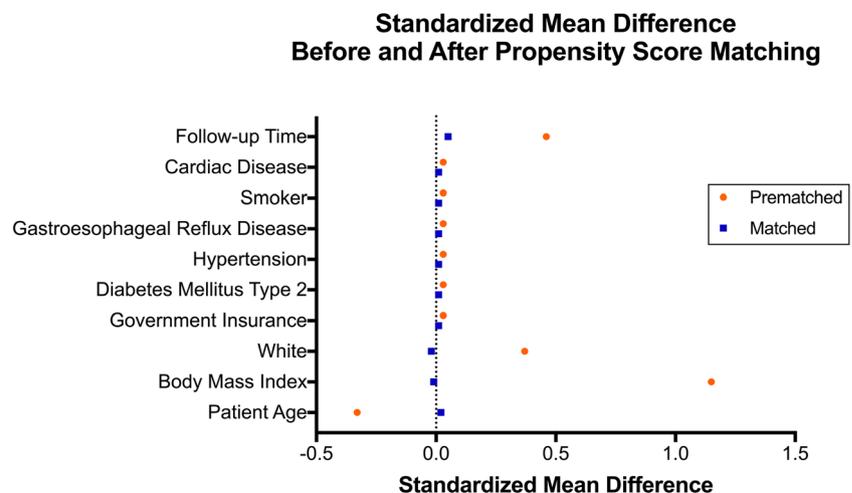
Patients were matched on a 1:1 basis with all model variables chosen a priori, including demographics (age, BMI, race), relevant comorbidities (diabetes mellitus, hypertension, gastroesophageal reflux disease, current smoking status, congestive heart failure/coronary artery disease), relevant preoperative substance use (tobacco), and time of follow-up. Balance was assessed by standardized mean difference (Fig. 1) with adequacy considered as less than 20% [18].

The primary outcome of interest was the overall incidence of breast cancer between surgical and non-surgical groups. Secondary outcomes included estrogen receptor (ER)-positive breast cancer incidence, as well as time to diagnosis and tumor characteristics among patients diagnosed with breast cancer. Tumor characteristics were not available for all patients. Univariate analyses were performed using chi-square or Fisher's exact tests for categorical variables and Wilcoxon rank sum test for continuous variables to assess for statistical differences in demographics, outcomes, and tumor characteristics between the surgical and non-surgical patients. Statistical significance was defined with the standard two-sided alpha value of  $< 0.05$ . Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

## Results

The cohort for this study included 32,539 female patients with morbid obesity. A total of 2753 female patients underwent

**Fig. 1** Standardized mean differences in included covariates before and after propensity score matching, revealing improvements toward 0.0 (no difference) after the match



bariatric surgery during the study period. The query of the institutional CDR identified 29,966 available female patients with initial outpatient visits for an initial diagnosis of morbid obesity. The baseline characteristics of all eligible surgical and non-surgical patients were compared. Patients who underwent bariatric surgery were significantly younger (42 years versus 48 years;  $p < 0.001$ ) and had a higher initial BMI (48.7 versus 39.1;  $p < 0.001$ ) than patients in the no surgery group. The rates of all comorbidities, excluding gastroesophageal reflux disorder (GERD), were also higher in the surgical group; however, the proportion of patients with government insurance did not differ between groups (Table 1).

To define patient inclusion for the analysis, the 1:1 propensity score match identified 2430 patients in each of the surgical and non-surgical cohorts with similar risk profiles. There were no significant baseline differences in median age (42.0 vs. 42.0 years;  $p = 0.29$ ), BMI (48.0 vs. 47.0 kg/m<sup>2</sup>;  $p = 0.41$ ), or medical comorbidities—aside from GERD—between the surgical and matched non-surgical control groups (Table 2). The median time of follow-up was longer for the surgical group as compared to the non-surgical group (6.0 vs. 5.0 years;  $p = 0.001$ ). The vast majority of surgical patients [1929 (79.4%)] underwent Roux-en-Y gastric bypass with smaller numbers undergoing gastric sleeve [183 (7.5%)], gastric banding [290 (11.9%)], and other procedures [28 (1.2%)].

There were significantly fewer diagnosed cases of breast cancer among the surgical patients [17 (0.7%) vs. 32 (1.3%);  $p = 0.03$ ] (Table 3). Breast cancer characteristics are displayed in Table 4. Receptor status was available for 11/17 surgical patients and 31/32 non-surgical patients. Histological subtype, nodal status, and staging information was available for 11/17 surgical patients and 29/32 non-surgical patients. Roux-en-Y gastric bypass was also the most common weight loss surgery

performed among the surgical patients diagnosed with breast cancer [12/17 (70.6%)].

Among the women diagnosed with breast cancer, the time to diagnosis did not differ between the surgical and non-surgical groups (5.1 vs. 4.2 years;  $p = 0.39$ ). The incidence of ER-positive breast cancer was significantly lower in the surgery group, with 36.4% of tumors in the surgical group testing ER positive compared to 71.0% in the non-surgical group. Rate of tumors positive for progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) did not differ between the two groups. There were also no differences detected in histological subtype of breast cancer, rate of positive lymph nodes, or stage of disease. Surgical patients did have a significantly smaller tumor size on pathology specimen (0.45 vs. 2.0 cm;  $p = 0.02$ ).

## Discussion

This propensity-matched analysis detected a decreased overall incidence of breast cancers among women with morbid obesity treated with bariatric surgery compared to no surgical intervention. Among the subset of women diagnosed with breast cancer, there was no difference in the time to diagnosis between the surgical and non-surgical groups. Notably, the incidence of ER positive tumors was lower in the surgical group. While there are multiple observational studies describing decreased incidence of cancer following bariatric surgery, the data available for specific cancer types remains limited [19, 20]. The current analysis represents one of few studies focusing specifically on breast cancer following bariatric surgery, and to our knowledge, the only study to additionally report tumor characteristics, including hormone and HER2 receptor status [17].

Obesity is an important risk factor for the development of multiple cancers [13, 21]. Suggested biological mechanisms include the promotion of chronic inflammation, increased steroid hormone production, and insulin resistance with resultant hyperinsulinemia [22]. In women, particularly following menopause when adipose tissue becomes a major source of estrogen synthesis, circulating levels of estrogens are strongly related to increased volume of body fat. This altered estrogen production has been shown to result in breast tumor estrogen levels up to ten times the concentration in the circulation [3, 23, 24]. As a result, both BMI and weight gain between ages 20 and 50 can be considered the most significant risk factors for breast cancer development aside from parameters included in the Gail model [25].

Intentional and significant weight loss, as occurs post-bariatric surgery, favorably modulates the same serum markers associated with cancer development and is likely responsible for the decreased incidence of cancers seen following bariatric surgery both in previous observational studies

**Table 1** Baseline characteristics between all eligible surgical patients and non-surgical controls

	Bariatric surgery <i>n</i> = 2753	No bariatric surgery <i>n</i> = 29,966	<i>p</i> value
Age (years)	42.0 (35.0–50.0)	48.0 (35.0–58.0)	< 0.001
White	2416 (87.8%)	21,969 (73.3%)	< 0.001
Initial BMI (kg/m <sup>2</sup> )	48.7 (44.0–55.0)	39.1 (36.5–43.6)	< 0.001
Government insurance	1046 (38.0%)	11,008 (36.7%)	0.19
DM type 2	744 (27.0%)	2557 (8.5%)	< 0.001
Hypertension	1340 (48.7%)	3898 (13.0%)	< 0.001
GERD	790 (28.7%)	912 (3.0%)	< 0.001
Current smoker	54 (2.0%)	836 (2.8%)	0.01
CHF/CAD	139 (5.1%)	935 (3.1%)	< 0.001

Categorical variables listed as *n* (%) and continuous variables listed as median (IQR)

BMI body mass index, DM type 2 diabetes mellitus type 2, GERD gastroesophageal reflux disease, CHF congestive heart failure, CAD coronary artery disease

**Table 2** Baseline characteristics between propensity-matched surgical and non-surgical groups

	Bariatric surgery <i>n</i> = 2430	No bariatric surgery <i>n</i> = 2430	<i>p</i> value
Age (years)	42.0 (35.0–51.0)	42.0 (31.0–53.0)	0.29
White	2119 (87.2%)	2138 (88.0%)	0.41
Initial BMI (kg/m <sup>2</sup> )	48.0 (43.0–53.0)	47.1 (40.6–55.5)	0.76
Government insurance	917 (37.7%)	906 (37.3%)	0.74
DM type 2	590 (24.3%)	616 (25.4%)	0.39
Hypertension	1069 (44.0%)	1052 (43.3%)	0.62
GERD	713 (29.3%)	149 (6.1%)	<0.0001
Current smoker	44 (1.8%)	39 (1.6%)	0.58
CHF/CAD	118 (4.9%)	106 (4.4%)	0.42

Categorical variables listed as *n* (%) and continuous variables listed as median (IQR)

*BMI* body mass index, *DM type 2* diabetes mellitus type 2, *GERD* gastroesophageal reflux disease, *CHF* congestive heart failure, *CAD* coronary artery disease

and the current analysis [26, 27]. We do not have access to the menopausal status of the women included in our study; however, given the initial median age and duration of follow-up, many of the women likely entered menopause by the end of the study period. As such, a decrease in the volume of adipose tissue following bariatric surgery should translate to a decreased concentration of circulating estrogen, potentially leading to the reduction in ER-positive tumors seen in the surgical group [26]. These findings are supported by a recently published prospective study of long-term outcomes following bariatric surgery which identified the most robust decrease in cancer incidence to be among a composite of female-specific malignancies sensitive to estrogen, including endometrial, ovarian, cervical, and breast cancers [15].

While we do not have data on the cumulative weight loss for patients in the surgical and non-surgical groups, bariatric surgery has been consistently shown to result in weight loss far superior to medical management alone [15, 28]. Our institution’s previously published 10-year weight loss outcomes following Roux-en-Y gastric bypass (RYGB) show improvements in annual percent reduction in excess BMI lost (EBMIL), with a peak of nearly 75% at 2 years and a maintained EBMIL of 52% at 10 years. Given these results and the high percentage of bariatric surgery patients undergoing RYGB at our institution, we extrapolate a substantial weight

**Table 3** Breast cancer diagnoses during available follow-up time in surgical and non-surgical groups

	Bariatric surgery <i>n</i> = 2430	No bariatric surgery <i>n</i> = 2430	<i>p</i> value
Time of follow-up (years)	6.0 (2.6–10.8)	5.0 (3.6–10.3)	0.001
Breast cancer	17 (0.7%)	32 (1.3%)	0.03

Categorical variables listed as *n* (%) and continuous variables listed as median (IQR)

loss effect in the current study’s surgical group, with relatively stable weight in the non-surgical group [11, 15].

Additional benefits of bariatric surgery with a potential impact on cancer incidence include improved glucose homeostasis with decreased insulin resistance. In addition to the substantial weight loss, RYGB patients at our institution sustained a persistent decrease in obesity-related comorbid disease, including diabetes mellitus, at 10 years of follow-up following surgery [11]. Given the durability of bariatric surgery-induced

**Table 4** Breast cancer characteristics in surgical and non-surgical groups

	Bariatric surgery	No bariatric surgery	<i>p</i> value
Time to diagnosis (years) ( <i>n</i> = 17; <i>n</i> = 32)	5.1 (1.7–9.3)	4.2 (1.8–6.9)	0.39
ER+ <sup>a</sup>	4/11 (36%)	22/31 (71%)	0.04
PR+ <sup>a</sup>	5/11 (46%)	22/31 (71%)	0.13
HER2+ <sup>a</sup>	3/11 (27%)	2/31 (7%)	0.07
Ductal histology <sup>a</sup>	9/11 (82%)	27/29 (93%)	0.29
Positive nodes <sup>a</sup>	0/11 (0%)	6/29 (21%)	0.26
Stage <sup>a</sup>			0.53
0	2/11 (18%)	7/29 (24%)	
1	7/11 (64%)	12/29 (41%)	
2	2/11 (18%)	7/29 (24%)	
3	0/11 (0%)	3/29 (10%)	
4	0/11 (0%)	0/29 (0%)	
Tumor size (cm) ( <i>n</i> = 8; <i>n</i> = 19) <sup>a</sup>	0.45 (0.3–1.9)	2.0 (1.4–3.0)	0.02

Categorical variables listed as *n* (%) and continuous variables listed as median (IQR)

<sup>a</sup>Descriptive tumor characteristics not available on all breast cancer patients (denoted by differing *n* for some variables)

*ER+* estrogen receptor positive, *PR+* progesterone receptor positive, *HER2+* human epidermal growth factor receptor 2

weight loss in a morbidly obese population as compared to intentional weight loss associated with medical management, the biochemical effects are also more likely to be sustained to provide a greater cancer benefit [17, 27].

This study is limited by the retrospective design and predominantly white patient population; however, use of propensity matching accounted for important baseline characteristics in both groups—including initial BMI and comorbidities common in patients with morbid obesity—though we were unable to account for other potential breast cancer specific risk factors, including hormone replacement therapy, oral contraceptive use, menopausal status, and family history. We were also unable to capture data on alcohol use, physical activity, and duration of obesity as well as more information regarding duration of smoking. Additionally, GERD was more prevalent among the surgical group, though this is likely attributable to the increased attention paid to these symptoms in bariatric surgery patients—as its presence affects the decision-making process between Roux-en-Y gastric bypass and sleeve gastrectomy—rather than a true difference in disease incidence.

The retrospective nature also introduces the possibility for misattribution of patients into the surgical or non-surgical cohort; however, we feel confident that patients in the non-surgical cohort did not undergo surgery at another institution given our access to their records at the termination of the included follow-up period. This also holds true for breast cancer diagnoses, and while it is possible that breast cancer cases diagnosed at an outside institution were missed, the risk of this error would be equivalent in the surgical and non-surgical groups.

As previously mentioned, we are unable to provide information regarding the weight loss experience of both the surgical and non-surgical groups. Attempting to accurately report BMI at the time of breast cancer diagnosis is highly susceptible to error, particularly in patients treated for their cancers at another institution. Additionally, the surgical group had a significantly longer median follow-up time. However, we would expect this bias toward the under-recognition of breast cancer in the non-surgical groups, potentially making our results an underestimation. Finally, as not all patients had their breast cancers diagnosed and treated at our institution, not all patients had tumor characteristics available for analysis.

## Conclusion

This propensity-matched study of women with morbid obesity identified a 0.6% decrease in the overall incidence of breast cancer—or a 46.2% relative risk reduction—for patients undergoing bariatric surgery as compared to non-surgical management of obesity. Additionally, among women diagnosed

with breast cancer, ER-positive tumors were significantly more common among the non-surgical patients. These data suggest the possibility of a breast cancer specific oncologic benefit to weight loss surgery, which is potentially most impactful for a reduction in ER-positive tumors. Given the tendency of younger, premenopausal women to undergo bariatric surgery, further study will be needed to determine the durability of this benefit and its potential implications on survival as these women progress through menopause.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Statement** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Consent Statement** For this type of study, format consent is not required.

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