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ORIGINAL CONTRIBUTIONS

Association of Bariatric Surgery Status with Reduced HER2+ Breast Cancers: a Retrospective Cohort Study

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Abstract

Background Bariatric surgery is associated with a reduced risk of developing certain malignancies, particularly in women. However, the impact of bariatric surgery on tumor characteristics, cancer treatment, and oncologic outcomes is unknown.

Method In a retrospective cohort study, 42 subjects diagnosed with breast cancer after bariatric surgery (1989–2014) were matched to 84 subjects with breast cancer (1984–2012) who did not undergo bariatric surgery, based on age, body mass index (BMI), and menopausal status at the time of breast cancer diagnosis, as well as the date of cancer diagnosis. Medical records were reviewed for cancer and bariatric endpoints. Statistical analysis was performed using mixed effects regression models, generalized estimating equation, conditional logistic regression, and Fisher's exact tests.

Results Women who developed breast cancer after bariatric surgery presented at an earlier stage compared to non-operated, obese controls. In the bariatric surgery group, there were fewer tumors with human epidermal growth factor receptor 2 overexpression (HER2+) (OR 0.16 (0.03–0.76); $p = 0.02$), with no significant differences seen in estrogen and progesterone receptor positivity. No HER2+ cancers were found in patients who underwent Roux-en-Y gastric bypass (OR 0.00 (0.00–0.43); $p = 0.002$). On multivariate analysis, bariatric surgery status remained associated with reduced HER2+ breast cancers (OR 0.18 (0.03–0.99); $p < 0.05$). At a mean follow-up of 5 years, bariatric surgery was associated with trends toward reduced cancer-specific and all-cause mortality.

Conclusions Bariatric surgery is associated with reduced HER2+ breast cancers, suggesting that bariatric surgery can influence breast cancer characteristics and, potentially, tumor biology.

Keywords Bariatric surgery · Breast cancer · Roux-en-Y gastric bypass · HER2 overexpression

Introduction

Obesity is associated with an increased risk of many cancers [1–4]. Previous studies have shown that sustained weight loss can decrease risk of multiple malignancies, such as esophageal adenocarcinoma, pancreatic, colon, endometrial, and breast cancers [5, 6]. In the USA, breast cancer is the most common cancer among women and the second leading cause of cancer-specific mortality in this group [7]. Postmenopausal weight gain has been established as an important risk factor for the development of breast cancer [8].

Bariatric surgery is the most effective and durable therapy for weight loss and obesity-related disorders [9, 10]. Several large cohort studies have demonstrated that bariatric surgery is associated with a reduction in cancer incidence and cancer-

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specific mortality in women [11–13]. However, while bariatric surgery is linked to a reduced risk of developing cancer, it is unknown whether bariatric surgery is associated with changes in tumor characteristics, treatments, or overall outcomes.

Breast cancer prognosis and treatment is largely dependent on the tumor stage and molecular profile. Stage is determined following surgical resection, while three separate receptors—estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)—are largely used to help guide adjuvant therapies. Classically, while the expression of tumor hormonal receptors like ER and PR offer a favorable prognosis, the expression of HER2 renders a poorer prognosis [14, 15]. However, the advent of newer targeted therapies for tumors with HER2 overexpression (HER2+) has improved survival in patients with these tumors [16, 17].

Obesity is associated with an increased risk of developing ER/PR-positive tumors in postmenopausal women [18, 19]. This risk may be secondary to high circulating levels of estradiol in the obese patients, in part due to increased aromatase activity in adipose tissue. Metabolic and endocrine changes of obesity, such as increased circulating insulin levels, may also drive cancer development and growth [20]. Lastly, obesity leads to aberrant inflammation within the breast adipose tissue, which can directly influence breast cancer biology [21].

Bariatric surgery reverses many of these metabolic, endocrine, and inflammatory pathologies that have been linked to changes in tumor biology. We therefore hypothesized that bariatric surgery status alters tumor characteristics in those patients who develop breast cancer, with associated changes in treatment and cancer-specific outcomes.

Methods

Study Groups

After obtaining Institutional Review Board approval, we designed a retrospective cohort study to compare breast cancer characteristics and outcomes in two groups: (1) Patients from a single tertiary center, the Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC), who underwent bariatric surgery (1989–2014; Roux-en-Y Gastric Bypass (RYGB), sleeve gastrectomy (SG), and laparoscopic adjustable gastric banding (LAGB)) and subsequently developed breast cancer. (2) Matched control subjects that developed breast cancer (1984–2012) and did not undergo bariatric surgery.

Inclusion criteria for our study group were (1) prior bariatric surgery, (2) age > 18 years, and (3) diagnosis of invasive breast carcinoma after bariatric surgery. Patients who had non-invasive breast cancer (lobar carcinoma in situ, ductal carcinoma in situ) were excluded due to differences in prognosis and management. Of over 5000 patients who underwent bariatric surgery, 42 patients were identified that developed subsequent invasive breast carcinoma.

Our control group was obtained from a total of 10,983 subjects from DF/BWCC who were diagnosed with breast cancer between 1984 and 2012. Patients who had a BMI less than 18, had non-invasive cancers, or had missing data on matching criteria were excluded, leaving a cohort of 5335 controls.

A one-to-two match was performed based on age, BMI, and menopausal status at the time of breast cancer diagnosis, as well as the date of cancer diagnosis. We separately matched pre- and post-menopausal subjects to have an exact match for menopausal status. Age was categorized into groups of 5-year intervals and BMI was categorized into groups with 3 kg/m^2 intervals. To control for significant management changes following seminal trials in breast cancer management, patients were pooled into two groups based on when their cancer was diagnosed—before or after 2005. In this way, surgical and control patients would receive treatments based on the same guidelines.

Subjects were matched using "Optimal Matching" package in R, which is a specific algorithm to sort similar subjects into non-overlapping matched sets, while separating treatment and control subjects too dissimilar to be compared. Subjects are selected to have the smallest average absolute distance across the matched pairs [22].

Primary and Secondary Outcomes

We primarily sought to identify differences in breast cancer characteristics including stage, grade, hormonal receptor status (ER and PR), HER2+, tumor size, and lymph node positivity. The guideline for the determination of HER2 overexpression was consistent for all subjects. HER2 expression was first tested by IHC and categorized based on staining intensity −0 (negative), 1+ (weakly positive), 2+ (moderately positive), and 3+ (strongly positive). Moderately positive tumors with confirmatory positive fluorescence in situ hybridization (FISH) and strongly positive tumors were considered as HER2+. Secondary outcomes included rates of breast conserving therapy, re-excision, trastuzumab, chemotherapy, hormonal therapy, radiation therapy, recurrence, breast surgery complications, choice of breast reconstruction in the patients who underwent total mastectomy, cancer-specific mortality, and all-cause mortality.

The data on trastuzumab, chemotherapy, hormonal therapy and radiation therapy were extracted from oncology clinic notes. Recurrence was defined as local or distant detection of breast cancer after an initial complete therapy over the course from initial cancer diagnosis to the last available oncology follow-up visit. Mortality was measured from the time of cancer diagnosis until the last documented inpatient or outpatient visit in the electronic medical record.

Statistical Analysis

Differences in demographic data were first examined using mixed effects regression models and generalized estimating equation where appropriate. Univariable and multivariable regression analyses of the outcomes were performed using conditional logistic regression and exact logistic regression where appropriate. Cancer-specific and all-cause mortality were analyzed by the Cox proportional-hazards regression model. Statistical analyses were carried out with the use of R statistical software version 3.3.2 and SAS statistical software version 9.4 (SAS Institute, Cary, NC). p values and 95% confidence intervals are two-sided, and p values less than 0.05 were considered to indicate significance.

Results

Our bariatric surgery group consisted of 42 subjects—31 patients underwent RYGB, 6 patients LAGB, and 5 patients SG (74%, 14%, and 12%, respectively). Table 1 shows demographic data for the matched controls. Age (55.4 vs. 54.9), BMI at the time of breast cancer diagnosis (34.9 vs. 34.8), menopausal status, and date of cancer diagnosis were well matched between the bariatric surgery and control groups, respectively ($p > 0.05$). In both bariatric surgery and control groups, the median length of follow-up from the time of cancer diagnosis to the last documented visit was 46 months. The median interval time between the bariatric surgery and breast cancer diagnosis was 48 months.

Bariatric Surgery Is Associated with Changes in Breast Cancer Characteristics and Outcomes

Women in the bariatric surgery group presented at an earlier stage compared to the non-surgical control group ($p = 0.05$, Table 2). However, bariatric surgery group did not show a significant difference in tumor grade as compared to controls ($p = 0.09$). As shown in Table 2, the proportion of the subjects who were diagnosed with breast cancer via routine screening tests were not significantly different between the bariatric surgery and control groups ($p = 0.17$), suggesting that earlier cancer detection does not explain differences in the presenting stage and grade.

Bariatric surgery was associated with a significantly reduced incidence of HER2+ cancers, and no statistical difference in ER+ or PR+ tumors. In a multivariable regression analysis adjusted for tumor stage, grade, and PR status, bariatric surgery remained significantly associated with reduced HER2+ breast cancers (Table 4). In the bariatric surgery group, 2 subjects were defined as HER2+ by IHC and none by FISH; however, in controls, this ratio was 12 by IHC and 6 by FISH.

Consistent with the differences seen in cancer stage and tumor characteristics, the use of chemotherapy, trastuzumab, and radiation therapy were significantly reduced in the bariatric surgery cohort compared to controls. There was no difference in the use of hormonal therapy between the groups. There were also no significant differences seen between groups in surgical treatment, including use of breast conserving therapy, need for re-excision, post-operative complications, or use of breast reconstruction (Table 3).

As seen in Fig. 1a, b, at a median follow-up of 46 months, there was a trend toward reduced breast cancer-specific and all-cause mortality in the bariatric surgery group when compared to controls; however, it did not reach significance (OR 0.13 (0.02–1.06), $p = 0.06$ and, OR 0.24 (0.05–1.06); $p = 0.06$, respectively). Moreover, no association between bariatric surgery and cancer recurrence was found (OR 0.64 (0.17–2.5); $p = 0.5$).

Subgroup Analysis of Breast Cancer Characteristics in RYGB Patients

Most bariatric surgery subjects underwent RYGB (74%), and these patients had the highest average weight loss compared to other procedures (mean BMI reduction in RYGB, LAGB, and SG are 12.9, 4.7, and 9.5 kg/m^2, respectively). Thus, a subgroup analysis for RYGB patients was completed.

Table 1 Characteristics of subjects in bariatric surgery and control groups

		Bariatric surgery ($n = 42$)	Control ($n = 84$)	p value
Age at the time of breast cancer diagnosis, years (SD)		55.4 (9.7)	54.9 (10.1)	0.66
BMI at the time of bariatric surgery, kg/m^2 (SD)		45.9 (7.9)	N/A	
BMI at the time of breast cancer diagnosis, kg/m^2 (SD)		34.9 (10)	34.8 (9.8)	0.74
Date of cancer diagnosis, *N*	≥ 2005	40	80	1
	< 2005	2	4	
Menopause, *N* (%)		26 (63)	52 (63)	1

SD standard deviation, *BMI* body mass index, *N/A* not applicable

Table 2 Primary outcome; breast cancer characteristics

		Bariatric surgery ($n = 42$)	Control ($n = 84$)	OR (%95 CI)	p value
Detected by routine screening, N (%)		32 (76)	54 (64)	1.84(0.77–4.43)	0.17
Stage, N (%)	I	28 (67)	41 (49)	REF	0.05
	II	9 (21)	26 (31)	0.53(0.22–1.27)	
	III and IV	5 (12)	17 (20)	0.45(0.15–1.32)	
Grade, N (%)	I	11 (26)	17 (20)	REF	0.09
	II	23 (55)	36 (41)	1.02(0.39–2.7)	
	III	8 (20)	31 (39)	0.42(0.13–1.23)	
Tumor size, cm		1.48	1.77	0.85(0.6–1.1)	0.27
LN+, N (%)		11 (26)	22 (27)	0.97(0.4–2.2)	0.9
ER+, N (%)		38 (90)	66 (78)	2.06(0.7–6.07)	0.19
PR+, N (%)		36 (85)	56 (67)	2.36(0.96–5.8)	0.06
HER2+, N (%)		2 (5)	18 (21)	0.16(0.03–0.76)	0.02*

OR odds ratio, *CI* confidence interval, *REF* reference, *cm* centimeter, *LN+* lymph node positive, *ER+* estrogen receptor positive, *PR+* progesterone receptor positive, *HER2+* human epidermal growth factor receptor 2 positive *represents statistical significance ($p < 0.05$)

In the RYGB subgroup, there remained similar differences in cancer stage and associated chemotherapy use as the overall bariatric surgery cohort; however, RYGB was not associated with changes in tumor grade or hormone receptor status (Supplement 1). In a univariable analysis, RYGB was associated with significant reduction of HER2+ tumors. In multivariable analysis adjusted for tumor stage, reduction in HER2+ tumors remained associated with RYGB status (Table 4).

Discussion

In several large observational studies and cohort studies of obese patients, bariatric surgery has been shown to be associated with a reduced incidence of multiple cancers [11–13]. This reduced cancer risk leads to an overall decreased cancer-specific mortality, and both risk and mortality reductions are driven by cancers that develop in women. In particular, the risk of postmenopausal breast cancer was significantly reduced in a recent, large cohort study of bariatric surgery patients [13].

Our study extends these prior observational studies by detailing the cancer characteristics of women who develop invasive breast cancer following bariatric surgery. We found that HER2+ tumors were less frequent in bariatric surgery patients, and no HER2+ cancers developed in post-RYGB patients. No significant differences in ER+ or PR+ cancers were detected. Bariatric surgery was also associated with earlier stage cancers.

While it is possible that bariatric surgery influences the rate and aggressiveness of tumor development, it is also possible that the earlier cancer stage seen in our bariatric surgery cohort is due to earlier detection of tumors. This earlier detection may reflect an increase in medical care sought or received by bariatric surgery patients or an improved ability to detect breast masses following weight loss. While we did not find significant differences in breast cancers diagnosed on routine

Table 3 Secondary outcome; breast cancer treatment outcomes

	Bariatric surgery ($n = 42$)	Control ($n = 84$)	OR (%95 CI)	p value
Chemotherapy, N (%)	13 (31)	50 (60)	0.26(0.11–0.62)	0.003*
Hormonal therapy, N (%)	31 (74)	62 (75)	1(0.41–2.43)	1
Trastuzumab, N (%)	2 (5)	17 (20)	0.17(0.04–0.81)	0.03*
Radiotherapy, N (%)	26 (62)	68 (81)	0.43(0.19–0.94)	0.03*
Breast conserving therapy, N (%)	26 (62)	38 (45)	2.04(0.91–4.57)	0.08
Breast surgery complications, N (%)	4 (9)	10 (13)	0.64(0.19–2.22)	0.5
Re-excision, N (%)	13 (31)	30 (37)	0.74(0.34–1.65)	0.47
Breast reconstruction surgery among patients with mastectomy, N (%)	12/16 (75)	23/40 (58)	2.11(0.39–11.3)	0.39

OR odds ratio, *CI* confidence interval *represents statistical significance ($p < 0.05$)

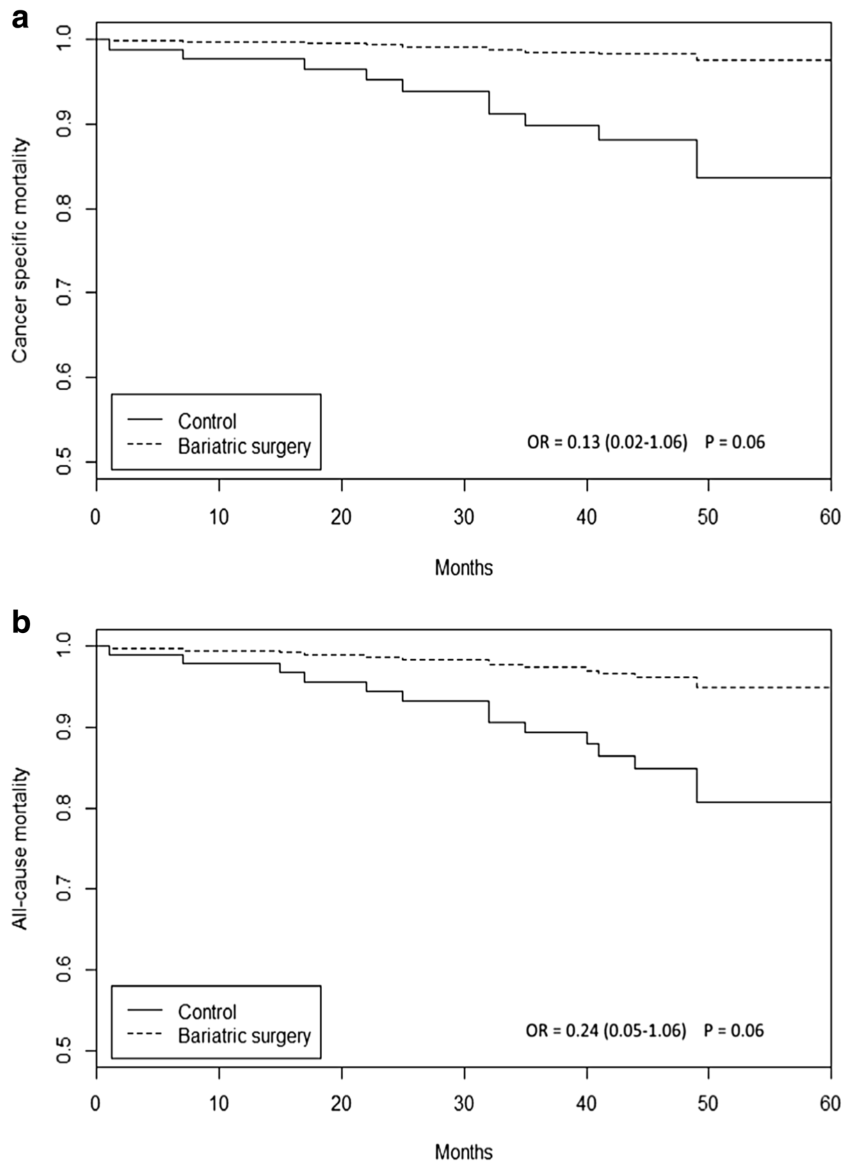

Fig. 1 Cancer-specific and all-cause mortality. Survival curve for breast cancer mortality comparing bariatric surgery group vs. controls (**a**). Survival curve for all-cause mortality comparing bariatric surgery group vs. controls (**b**)

screening in our two groups, we cannot exclude unmeasured differences in the cohorts that influence time to cancer diagnosis.

Notably, HER2+ in breast cancer is independent of stage. So, potential bias toward earlier tumor detection in the bariatric surgery group would not be predicted to impact the frequency of HER2+ cancers in our study. Moreover, on multivariable analysis, adjusted for all variables that showed a trend on univariable analysis, both bariatric surgery and RYGB status remained independently associated with reduced HER2+ tumors.

In animal models, calorie restriction reduces the incidence of HER2+ breast tumors, a finding that correlated with changes in epigenetic reprograming and ER expression [23]. Bariatric surgery not only reverses obesity but also positively impacts systemic and adipose inflammation, metabolism, and diet composition: all pathways that have been shown to impact breast cancer biology in obesity [24–28]. Therefore, it is biologically plausible that bariatric surgery might alter breast tissue microenvironment and thereby influence breast cancer characteristics.

Table 4 Multivariable regression analysis of HER2 overexpression and bariatric surgery or RYGB status

	OR (95% CI)	*p* value
HER2+ (Bariatric surgery vs. control)	0.18(0.03–0.99)	0.049*
HER2+ (RYGB vs. control)	0.09(0–0.46)	0.008**

*Adjusted for stage, grade, progesterone receptor positivity (PR+)

**Adjusted for stage

OR odds ratio, *CI* confidence interval, *HER2+* human epidermal growth factor receptor 2 positive

Aside from stage and HER2+, tumor ER and PR status influence breast cancer prognosis and guide therapy. Obesity is associated with hormone receptor–positive breast cancers in postmenopausal women. In our study, we did not find a significant link of bariatric surgery with ER+ or PR+ tumors. However, our study reflects the usual bariatric surgery population, and therefore may be underpowered to detect effects on hormone receptor status, particularly in postmenopausal patients. Moreover, it is likely that at least some of the breast cancers may have been developing in patients before bariatric surgery, while still under the influence of the hyper-estrogen state of obesity, and only progressed to clinical detection after surgery and weight loss.

Recent studies have documented an increased risk of complications following both unilateral mastectomy and subsequent breast reconstruction with increasing BMI [29, 30]. At a matched BMI, our bariatric surgery and control cohorts had equivalent surgical outcomes, including use of breast conserving therapy, plastic surgical reconstruction, need for tumor re-excision, and surgical complications. However, our bariatric surgery group lost, on average, 11 kg/m^2, before their cancer and reconstructive surgery. Therefore, one might predict that bariatric surgery improved surgical outcomes through weight loss—a hypothesis that would be interesting to study in the future.

Our study has several limitations. First, while this is the largest and most detailed study of breast cancer in bariatric surgery patients to date, our sample size and follow-up length remain modest. As mentioned previously, this study is underpowered to detect smaller influences of bariatric surgery on breast cancer hormone receptor status, recurrence, and survival. Nevertheless, we detected a trend toward improved cancer-specific survival in the bariatric surgery cohort, consistent with their less pathologically aggressive tumor characteristics. Second, we cannot exclude that our findings reflect inherent differences in the bariatric surgery cohort for which we were unable to control. Lastly, we were unable to assess whether the impact of bariatric surgery on breast cancer characteristics was related to weight loss, dietary changes, or the other metabolic, endocrine, and immunologic changes known to occur following bariatric surgery. Despite these limitations, our findings support previous studies that link obesity and breast cancer biology and extend them by providing new evidence that bariatric surgery may, in fact, influence breast cancer characteristics.

Conclusions

We describe an association of bariatric surgery with earlier stage, HER2-negative breast cancers. Given the growing links between obesity and tumor biology, further study to characterize the impact of bariatric surgery on breast cancer is warranted.

Compliance with Ethical Standards

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

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