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Bariatric

Bariatric surgery is independently associated with a decrease in the development of colorectal lesions

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ABSTRACT

Background: Obesity is a risk factor for colorectal cancer and possibly the formation of precancerous, colorectal polyps . Bariatric surgery is very effective for long-term weight loss; however, it is not known whether bariatric surgery decreases the risk of subsequent colonic neoplasia. We hypothesized that bariatric surgery would decrease the risk of developing colorectal lesions (new cancer and precancerous polyps).

Methods: We reviewed all patients ($n = 3,676$) who underwent bariatric surgery (gastric bypass, sleeve gastrectomy, or gastric banding) at the University of Virginia (Charlottesville, VA) 1985–2015. Obese, nonoperative patients ($n = 46,873$) from an institutional data repository were included as controls. Cases and controls were propensity score matched 1:1 by demographics, comorbidities, body mass index, and socioeconomic factors. The matched cohort was compared by univariate analysis and conditional logistic regression.

Results: A total of 4,462 patients (2,231 per group) with a median follow-up of 7.8 years were well-matched with no statistically significant baseline differences in initial body mass index (48 vs 49 kg/m^2), sex, and age in addition to other comorbidities (all $P > .05$). The operative cohort had more weight loss (55.5% vs −1.4% decrease in excess body mass index, $P < .0001$). The operative cohort developed fewer colorectal lesions (2.4% vs 4.8%, $P < .0001$). We observed no differences in polyp characteristics or staging for patients who developed cancer (all $P > .05$). After risk adjustment, bariatric surgery was independently associated with a decrease in new colorectal lesions (OR 0.62, 95% CI 0.42–0.91, $P = .016$).

Conclusion: Bariatric surgery was associated with lesser, risk-adjusted incidence of new colorectal lesions in this large population of propensity matched patients undergoing bariatric surgery compared with a control group not undergoing bariatric surgery. These results suggest the benefits of bariatric surgery may extend beyond weight loss and mitigation of comorbidities.

Introduction

As more patients elect to undergo bariatric surgery for long-term weight loss, there is a lack of definitive evidence to show the effect of bariatric surgery on the future development of obesity-related cancers. Only a few studies have been published on the effect of bariatric surgery on colorectal cancer (CRC) or premalignant polyp formation, and the few that have been published show contradictory findings. Some studies report a statistically significant decrease in the formation of CRC[1,2] and colorectal polyps[3] after bariatric surgery, and others show a decrease in all obesity-related cancers but not in CRC specifically.[4] At the same time, other studies have shown that bariatric surgery led to an increase of CRC[5–7] but not in other hormone-related cancers.[5,7] More confusing, still, is the reported difference in outcome of CRC between women and men.[4,8,9] The issue with some of these studies is the short post-operative follow-up period of less than 5 years, which would not allow for adequate malignant carcinogenesis.[3,4,10] Also, 2 of the 3 studies that found negative correlations with bariatric surgery and CRC risk are from the same, register-based Swedish patient cohort,[6,7] possibly introducing a population bias in their results. Neither of these studies performed case matching with control

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patients on factors other than demographics to include important CRC risk factors, such as inflammatory bowel disease (IBD) and use of alcohol and tobacco.

The pathophysiology of the development of CRC or the protection against the development of CRC is also poorly understood because of conflicting published data. When investigating rectal mucosal biopsies from patients who underwent Roux-en-Y gastric bypass (RYGB), one British institution showed increases in the size and number of mitoses of cells in the rectal crypts as a marker for an increased proliferation of these cells,[11,12] but a British cohort at another institution showed a decrease in the proliferation of these cells.[13] This contradiction may be a result of very short follow-up times from 6 months to 3 years in all 3 studies, which further obscures the possible influence of bariatric surgery on the development of or protection against CRC.

Overall short follow-up intervals and the lack of standardization between bariatric patients and appropriate controls risk adjusted for important CRC risk factors may contribute to these conflicting results. We hypothesized that bariatric surgery would decrease the risk of developing new CRC or precancerous colorectal polyps. By performing propensity case-matched cohorts and using a greater number of case-match variables to include not only demographics but also initial body mass index (BMI), follow-up period, several comorbidities, and social histories, we would be able to better understand the effect of bariatric surgery on the development of CRC.

Methods

Patients

The Institutional Review Board of the University of Virginia (Charlottesville, VA) approved this study (#17132) by waiving the consent requirement because of its retrospective nature. All adult patients who underwent bariatric surgery (including RYGB, sleeve gastrectomy, and adjustable gastric banding) for morbid obesity (n = 3,676) at our single academic institution between 1985 and 2015 were identified retrospectively from a prospectively maintained database.[14] To identify an appropriate control group, an institutional clinical data repository (CDR) of all routine outpatient visits was queried to identify a nonoperative cohort of 46,873 morbidly obese patients who did not undergo weight-loss surgery. Propensitymatched groups were then generated to facilitate adjusted comparisons between the operative and nonoperative 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. Patients were excluded if they were younger than 18 years of age, incarcerated, or had incomplete medical records. These baseline characteristics were collected at the time of initial diagnosis of morbid obesity (BMI $\geq$ 35 kg/m^2) entered into the electronic medical record for nonoperative control patients and at the time of the preoperative appointment for the patients undergoing bariatric surgery. Subsequent BMI measurements were captured, as available, by the most recent BMI measurement recorded at the time of the diagnosis of CRC or detection of a colorectal polyp. Diagnoses of CRC or colorectal polyp(s) were identified through the CDR for both operative and non-operative patients before and after the time of bariatric surgery or diagnosis of obesity in the control group. New diagnoses of CRC or colorectal polyps were captured even if patients were treated at outside institutions. For all patients with a diagnosis of CRC or colorectal polyps, tumor characteristics were identified when available via review of the electronic medical record, including pathology reports from outside institutions if applicable. The term “colorectal lesion” was used to include both CRC and colorectal polyps.

Statistical analyses

Patients were matched on a 1:1 basis with all model variables chosen a priori, including demographics (age, initial BMI, race), history of colorectal polyps or CRC, 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. Adequacy of the match was assessed by balance metrics, including standardized mean difference and histograms of propensity scores.[15]

The primary outcome of interest was the overall incidence of CRC or colorectal polyps between the operative and nonoperative groups. Secondary outcomes included the incidence of CRC, development of colorectal polyp, and tumor characteristics among patients diagnosed with CRC. Complete tumor characteristics were not available for all patients. Univariate analyses were performed using the χ^2 or Fisher 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 operative and nonoperative patients. Within the propensity matched cohort, multivariate logistic regression was used to assess the association between bariatric surgery and the incidence of colorectal lesions. Variables in the model were selected a priori based on clinical risk factors for colorectal lesions, and performance of the model was assessed by calculating the area under the curve. Statistical significance was defined with the standard, two-sided α value of <0.05. Statistical analyses were conducted using SAS v 9.4 (SAS Institute, Cary, NC).

Results

A total of 3,410 patients undergoing bariatric surgery were initially evaluated and compared with 45,750 obese control patients who did not undergo bariatric surgery from the same institutional data repository (Supplemental Table I). Both patient groups varied in almost all demographic and comorbidities evaluated.

A total of 2,231 patients were matched in each group (Table I). The 2 groups were well matched in all baseline characteristics except for sex (Figure) with histograms of matched propensity scores shown in Supplemental Figure 1. Of the 2,231 bariatric surgery patients, 165 (7.4%) patients had sleeve gastrectomies, 1,719 patients (77.1%) had RYGB, 303 patients (13.6%) had bandings, and 44 patients (2%) had other bariatric operations. We observed no baseline differences between matched groups in initial BMI (48 versus 49 kg/m^2, $P = 0.26$), female sex (82.7% versus 84.4%, $P = .16$), and age (42.6 versus 42.8 years, $P = .63$) in addition to other comorbidities (all $P > .05$, Table I). The only covariates within the propensity score that still remained statistically significant was a history of psychologic disorders (13.7% vs 6.3%, $P < .001$) and degenerative joint disorders (20.2% vs 17.4%, $P = .02$), where the bariatric surgery group had greater rates compared with the control group. We included both covariates in our propensity score because psychologic disorders and degenerative joint disorders have not been found to be associated with the development of colorectal lesions.[16]

The median follow-up period for both matched groups was approximately 7.8 years. The difference of follow-up time in days

Table I
Comparison of the propensity-matched bariatric surgery and non-operative groups*

	No bariatric surgery $n = 2,231$	Bariatric surgery $n = 2,231$	P value
Age (y)	42.8 (13.4)	42.6 (10.3)	.63
Female	1,882 (84.4%)	1,846 (82.7%)	.16
White	1,954 (87.6%)	1,939 (86.9%)	.53
Initial BMI (kg/m^2)	49.3 (11.4)	48.3 (8)	.26
Government insurance	892 (40%)	871 (39%)	.54
DM Type II	508 (22.8%)	501 (22.5%)	.83
IBD	21 (0.9%)	19 (0.9%)	.87
Hypertension	902 (40.4%)	894 (40.1%)	.83
GERD	1,069 (47.9%)	1,058 (47.4%)	.76
Current alcohol use	33 (1.5%)	40 (1.8%)	.48
Current smoker	553 (24.8%)	609 (27.3%)	.06
CHF/CAD	109 (4.9%)	109 (4.9%)	1.00
COPD	65 (2.9%)	57 (2.6%)	.52
OSA	141 (6.3%)	168 (7.5%)	.13
Degenerative joint Disorder	389 (17.4%)	450 (20.2%)	.02
History of colorectal lesions	42 (1.9%)	50 (2.2%)	.46
New colorectal lesions	107 (4.8%)	54 (2.4%)	*< .0001*

BMI, body mass index; *DM Type II*, diabetes mellitus type II; *IBD*, inflammatory bowel disease; *GERD*, gastroesophageal reflux disease; *CHF*, congestive heart failure; *CAD*, coronary artery disease; *COPD*, chronic obstructive pulmonary disease; *OSA*, obstructive sleep apnea.
* Categorical variables presented as *N* (%) and continuous variables presented as median (IQR).

after bariatric surgery compared with after the diagnosis of obesity was 2,745 vs 2,944 days ($P < .001$). Although this difference of 6.6 months is statistically significant, the clinical importance is believed to be minimal for the development of CRC. As expected, the matched bariatric group had considerably more weight loss than the matched control group at the time of diagnosis of the colorectal lesion (55.5% vs −1.4%; $P < .0001$).

From the time of bariatric surgery or the diagnosis of obesity in the controls, the percentage of patients in the bariatric group were noted to have developed fewer total colorectal lesions, (a new diagnosis of CRC or colorectal polyps, 2.4% vs 4.8%, $P < 0.0001$) despite no differences in the history of colorectal lesions before these time points. More specifically, we observed no differences in the number of new polyps formed, polyp characteristics, or stage of the new CRC for patients who developed cancer in either group (Table II). At the time of the initial diagnosis of CRC, metastases were found in 3 of the 5 patients (60%) in the bariatric group ,with 0 patients in the control group ($P = .04$).

After further risk adjustment using conditional logistic regression, bariatric surgery was independently associated with a decrease in the formation of new colorectal lesions by 38% (OR 0.62, 95% CI 0.42−0 .91, $P = .016$, Table III). Other clinical factors, including age, were also found to be independently associated with developing new colorectal lesions (OR 1.06, 95% CI 1.03−1.09, $P \leq .0001$).

Discussion

Bariatric surgery was associated with lesser risk-adjusted incidence of the diagnosis of new colorectal lesions by 38% compared with propensity matched controls who did not undergo bariatric surgery in this large cohort of patients, with a mean follow up of 7.8

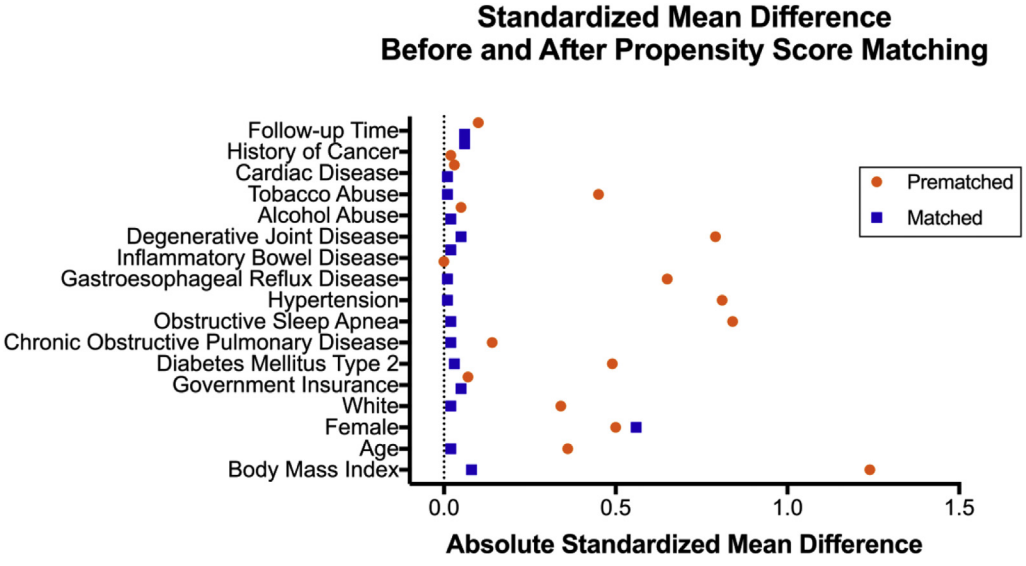

Figure. Balance assessment before and after propensity score matching, showing the absolute standardized mean difference.

Table II
Characteristics for new colorectal lesion for matched cohort*

	No bariatric surgery $n = 107$	Bariatric surgery $n = 54$	P value
New colorectal polyps	101 (94.4%)	49 (91%)	.39
Number of polyps (mean)	2	2	.97
Polyp size (mm)	8 (8.2)	7 (6)	.77
Polyp classification			
Tubulovillous adenoma	7 (6.5%)	5 (9%)	.54
Adenomatous polyp	2	2	.48
Tubular adenoma	55 (51.4%)	31 (57%)	.47
Sessile	32 (30%)	13 (24%)	.44
Sessile serrated, nondysplastic	7 (6.5%)	3 (6%)	.81
Hyperplastic polyp	48 (44.9%)	20 (37%)	.34
New colorectal cancer	6 (5.6%)	5 (9%)	.39
Clinical stage			.16
1	1	1	
2	0 (0%)	1	
3	4 (3.7%)	0	
4	0 (0%)	3 (6%)	
T stage			.20
T1	0 (0%)	1	
T2	2 (1.9%)	0	
T3	2 (1.9%)	4 (7%)	
T4	1 (0.9%)	0	
Metastasis present at diagnosis	0 (0%)	3 (6%)	.04
Number of lymph node involved			.23
0	1	3 (6%)	
1	2	0	
2	2	1	
3	0	1	
Genetic mutation present	0	2	.11
Family history of cancer	17 (15.9%)	9 (17%)	.11

BMI, body mass index; *DM Type II*, diabetes mellitus type II; *GERD*, gastroesophageal reflux disease; *CHF*, congestive heart failure; *CAD*, coronary artery disease.
* Categorical variables presented as *N* (%) and continuous variables presented as median (IQR). Percentages are relative to the group column for each clinical variable.

years. We found no difference in the number of new polyps formed, types of polyps found, or overall CRC TNM staging between the patients in each group who developed a new colorectal lesion; however, none of the control patients had evidence of metastases at the time of the new CRC diagnosis; whereas metastases were present in 3 of the 5 (60%) new CRC patients in the bariatric group. The low number of new CRC in both cohorts makes any conclusion about the clinical implication related to these observations impossible.

Weight loss has been shown to have a protective effect related to decreases in oxidative damage to deoxyribonucleic acid and ribonucleic acid of white blood cells and increasing telomere length of rectal mucosa samples.[17] In addition, the decreased systemic inflammation[18] and hyperinsulinemia[13] after bariatric surgery may also contribute to its protective effect on formation of CRC. It would be interesting to understand this effect during long-term follow-up to further understand whether the CRC protective effect we found in this study is attributable to bariatric surgery or its subsequent weight loss.

Table III
Conditional logistic regression for risk of developing new colorectal lesions*

Risk factors	Odds ratio	95% CI		P value
Bariatric surgery	0.62	0.42	0.91	.016
Female	0.71	0.32	1.60	.415
White	1.01	0.46	2.21	.978
Initial BMI	1.01	0.98	1.05	.473
Age	1.06	1.03	1.09	< .0001
IBD	1.12	0.81	1.29	.992
Private insurance	1.23	0.88	1.83	.495

BMI, body mass index; *IBD*, inflammatory bowel disease.
* c-statistic = 0.719.

The various types of bariatric surgery may also affect the overall protective effects against the development of colorectal lesions. Not only have there been conflicting histologic results for RYGB published, one study found that RYGB appeared to increase the risk of CRC, but this ostensible effect was not apparent after gastric banding or sleeve gastrectomy.[5] In contrast, there appeared to be an increased risk of CRC with a cohort of patients undergoing bariatric surgery which involved a majority of banding procedures.[6,7] Because gastric bandings have been shown to have lesser overall weight loss compared with gastric sleeves and RYGB,[19,20] the increased risk of CRC found may be attributable to the lack of marked weight loss in the majority of patients in both studies. In addition to the effect of weight loss, changes in the gut microbiome,[21] malabsorption, or alterations of circulating gastrointestinal hormones after RYGB compared with other bariatric procedures[22] may play a possible role in this increased risk of CRC.

Other variables in the conditional logistic regression that were found not to have any association with CRC lesions are a history of IBD and the initial BMI despite both being known risk factors for CRC.[16,23] For IBD, this may be attributable to a longer follow-up period needed from polyp to CRC development. In terms of the initial BMI, this value was recorded at the time of bariatric surgery or at the time of the first documented obesity diagnosis for the control group. This approach does not suggest, however, that BMI in general would not affect the development of CRC lesions. Because BMI was not recorded serially during the follow-up period in both groups for this retrospective review, it is unclear whether this protective effect is attributable to the weight loss seen in the bariatric group, as discussed earlier, or attributable to bariatric surgery itself.

Our study is limited by the retrospective design; however, propensity matching was used to minimize any differences in

important baseline characteristics in both groups, including the initial BMI and other comorbidities common in patients with morbid obesity. Because of the large disparity in sex in the bariatric surgery group versus the control group, which was not part of the propensity matching, this characteristic remained unbalanced after matching; however, this difference was adjusted for with conditional logistic regression. We are unable to provide information regarding weight loss at specific time intervals postoperatively in the operative group compared with similar time intervals in the control group during follow up because these data were unavailable. Another limitation is that only colonoscopies performed at our institution were included to describe the characteristics of the CRC lesions diagnosed, however, all new diagnoses of polyps or colorectal cancer were accounted for irrespective of where the colonoscopy was performed. If a selection bias was present in the bariatric group, increased surveillance within this group still accounted for a decrease in the diagnosis of both CRC and polyp formation during the follow-up. Finally, the nonoperative group had a somewhat greater median follow-up time, but we maintain that the difference of 6 months over a 7-year follow-up period is likely not clinically relevant.

As current bariatric procedures result in consistent, long-term weight loss compared with more conservative medical regimens of weight loss, bariatric surgery may be protective against the development of CRC during the lifetime of obese patients. These results are encouraging in that the benefits of bariatric surgery may extend beyond weight loss and beyond just the decrease in the comorbidities related to obesity.

Conflict of interest

The authors have indicated that they have no conflict of interest regarding the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.03.013.

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