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Association between Weight Loss and the Risk of Cancer after Bariatric Surgery

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Abstract

Objective—The goal of this study was to determine whether the reduction in cancer risk after bariatric surgery is due to weight loss.

Methods—We conducted a retrospective matched cohort study of patients undergoing bariatric surgery using data from a large integrated health insurance and care delivery system with five sites in four states. The study included 18,355 bariatric surgery subjects and 40,524 non-surgical subjects matched on age, sex, BMI, site and Elixhauser comorbidity index. Multivariable Cox proportional hazards models examined the relationship between weight loss at 1 year and incident cancer up to 10 years follow-up.

Results—We identified 1,196 incident cancers. The average one year post-surgical weight loss was 27% among patients undergoing bariatric surgery vs 1% in matched non-surgical patients. Percent weight loss at one year was significantly associated with a reduced risk of any cancer in adjusted models (HR 0.897, 95% CI 0.832–0.968, p=0.005 for every 10% weight loss) while bariatric surgery was not a significant independent predictor of cancer incidence.

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Conclusions—Weight loss after bariatric surgery was associated with a lower risk of incident cancer. There was no apparent independent effect of the bariatric surgery itself on cancer risk that was independent of weight loss.

Keywords

Bariatric Surgery; Weight Loss; Cancer

Introduction

Obesity is a well-established risk factor for developing cancer and has been estimated to contribute to 9.4% of all cancers in women and 3.5% of all cancers in men within North America.[1, 2]. Obesity is associated with 15–20% of all cancer deaths[3]. Multiple biologic mechanisms have been proposed for the link between obesity and cancer including increased insulin and insulin-like growth factors[4], increased estradiol[5–8], mechanical mechanisms[9], and inflammation[10]. These biologic mechanisms associated with obesity that lead to a risk in cancer risk are potentially modifiable by weight loss. After weight loss either by diet or exercise, adipose-tissue gene expression changes at six months for both steroid-hormone metabolism and IGF signaling[11]. Additionally, over 60 studies have demonstrated that diet and exercise decrease inflammatory biomarkers that may potentially decrease the risk of cancer over time[12].

Two large studies examined the relationship between medical weight loss and cancer. The first, a prospective cohort study of 21,707 women in the Iowa Women's Health Study, demonstrated that a history of intentional weight loss of over 9 kilograms was associated with an 11% reduction in the risk of cancer[13] and that weight loss before or after menopause conferred a reduction in the risk of postmenopausal breast cancer[14]. Additionally, The Nurse's Health Study demonstrated that a 10 kilogram weight loss was associated with a decreased risk of postmenopausal breast cancer[15].

Multiple studies have shown that bariatric surgery is associated with a reduced risk of cancer[16–20]. However, it remains unclear if the reduction in cancer risk is related to bariatric surgery itself or the weight loss induced by bariatric surgery. In the case of type 2 diabetes remission following bariatric surgery, it has been proposed that bariatric surgery may have beneficial effects on glycemic control that are independent of weight loss and mediated by several factors, including changes in gut hormones, bile acids, and the microbiome[21]. Whether there are similar surgery-specific mechanisms in the context of reduced cancer incidence following surgery is unknown. It is possible that similar weight independent effects of bariatric surgery impact cancer risk.

The goal of this study was to determine whether the reduction in cancer risk is entirely related to weight loss or if there is evidence for an effect of bariatric surgery that is independent of weight loss. It is hypothesized that there is an independent effect of bariatric surgery after accounting for the amount of weight loss after surgery.

Methods

A retrospective observational matched cohort study was conducted using data from electronic health record databases and registries from five Kaiser Permanente regions, representing a large integrated health insurance and care delivery systems with five study sites: Kaiser Permanente (regions of Southern California, Northern California, Northwest (Oregon), Colorado and Washington (formerly, Group Health Cooperative). The cohort included obese individuals who were enrolled in any of the above health plans between January 1, 2005 and December 31, 2012. Follow-up extended through 2014. Institutional review board approval, including waiver of informed consent, was obtained at Kaiser Permanente Colorado and all other sites ceded IRB review to the KP Colorado IRB.

Patients who underwent bariatric surgery were identified using CPT-4 and ICD-9 codes for surgery between January 1 2005, and December 31, 2012. Of 33,141 patients identified to have had bariatric surgery, 10,882 were excluded for not meeting study criteria: prior bariatric surgery (902); not enrolled for 12 months prior to surgery (3,339); older or younger than 18–79 at time of surgery (152); pre-surgical history of cancer (2,492); and without BMI measurement within 12 months of surgery (3,997). Each of the remaining 22,259 bariatric surgery patients were then matched to patients who had never had bariatric surgery using the following matching criteria: Kaiser Permanente region; sex; birthdate within one year; body mass index; and Elixhauser comorbidity index[22]. Non-surgical patients were provisionally matched to multiple surgical patients based upon region, sex and birthdate within one year. Potential matches were then excluded if they had a prior cancer or if the BMI was not within 5% of the surgical patient. Each surgical patient was matched to 3 nonsurgical patients based on the smallest difference in Elixhauser comorbidity index score when possible. If the Elixhauser difference was 3 or greater, the matches were removed and returned to the pool of potential matches. In a second phase of matching for those surgical patients without 3 non-surgical matches, the BMI matching window was extended to +/− 10% of the surgical patient's BMI. This second phase yielded 2.85% of the matches. After the final matching process, only 62 surgical patients remained without a match. Next, surgical patients and their non-surgical matched patients were eliminated from the final cohort if they did not have at least 18 months of follow-up time after the index date. The index date was defined as the date of surgery for each surgical patient; and, for each nonsurgical patient, the matched surgical patient's surgery date was assigned as the index date. Finally, patients were eliminated from the final cohort if they did not have weight measurements within 12 months each side of the 12 month follow-up.

Estimated percent weight loss was calculated for one year after surgery for bariatric surgery patients or one year after the index date for non-surgical matches using linear interpolation. Two recorded weights for each patient were used, along with the dates on which the weights were recorded. The two weights were the last one prior to the 12 month post-index date and the first one following the 12 month post-index date. That is, the two weights closest to 12 months after the index date. The estimated weight at 12 months post-index date was then the linear interpolation across time between the two recorded weights just described. The difference between this estimated weight and the baseline weight (last pre-index date weight) was then used to calculate percent weight lost for each patient. The robustness of this method was supported by the following results: The mean (sd) time between the recorded weight prior to the 12 month follow-up was 2.8 (2.8) months, and time to the weight following the 12 month follow up was 2.3 (2.6) months. In the surgical patients, the mean (sd) percent weight loss at the first post-12 month weight measurement was 27.7% (9.9), while the mean (sd) estimated 12 month percent weight loss was 27.3% (9.3). The similarity of these means that, on average, weight was not declining much at or after 12 months post-surgery. The correlation across patients between the 12 month estimated weight and the first post-12 month measurement was 0.975, indicating that the slow average weight decline around the 12 month post-surgery time point was highly consistent across patients. Thus, at 12 months, weight was declining only slightly among the surgery patients, and the variability across patients in the weight slope at 12 months was small. For the nonsurgical matches, the weight trajectories were flat, and therefore not subject to appreciable methods variance when comparing different methods of 12 month weight loss estimation.

Incident cancers were identified from Kaiser Permanente tumor registries at each institution. Obesity-related cancers (breast (postmenopausal), colon and rectum, corpus uteri, esophagus (adenocarcinoma), gallbladder, gastric cardia, kidney (renal-cell), liver, meningioma, multiple myeloma, ovary, pancreas and thyroid) were defined based on evidence deemed sufficient for an association with obesity according to a report by the International Agency for Research on Cancer (IARC)[23]. All other cancers were considered not associated with obesity.

To characterize the study sample, means, medians and frequencies for variables used as covariates in the Cox proportional hazards models as well as other factors of interest were calculated. Subjects with a history of bariatric surgery were compared to the matched nonsurgical patients using standardized differences. Cox proportional hazards models were used to examine the relationship between weight loss at 1 year, bariatric surgery and incident cancer. To eliminate the potential for a reversed causal process in which cancer might cause weight loss, patients' time under observation was started at 18 months post-surgery using only those patients who were cancer free until that time. Separate models were estimated predicting the development of any cancer, obesity associated cancers and non-obesity associated cancers with observations censored at the diagnosis of cancers not of the type being predicted, as well as when patients became unenrolled in the health plan. Covariates used in the adjusted models using all patients are listed where appropriate. Adjusted analyses of either only surgery patients or only matched non-surgery patients employed the additional covariates of those factors that had been used in the matching.

Since percent weight loss and bariatric surgery were highly collinear, hazard ratios for the risk of cancer for those receiving bariatric surgery and those with no surgery were also estimated separately. For each outcome (all cancers, obesity related cancers and non-obesity related cancers), both unadjusted models and non-parsimonious models adjusted for the covariates that potentially impact cancer risk were estimated. We tested for linear interactions between surgery status and weight loss in models containing only those two main effects, as well as in the same models with covariates added. This was done for all cancers, and for obesity and non-obesity related cancers. Within this set of models we tested the proportional hazards assumption by adding interactions between time and each of surgery status and weight loss, in simple models containing only those factors. In those same models the linearity of weight loss effects was tested by adding to the models a quadratic weight loss term. In the models estimated on surgery cases only or controls only, tests of proportional hazards and linearity of weight loss were tested by adding the necessary terms to models containing weight loss only. Robust sandwich estimators were used to account for the matching. The alpha for all tests was a two-tailed p=0.05, unadjusted for multiple tests, and all analyses were performed using SAS v9.4 (Cary, NC).

Results

The final matched cohort had 18,355 bariatric surgery patients and 40,524 non-surgical matched patients. Over 80% were female with an average age of 46 years. The two groups were well balanced on both the presence of obesity associated conditions and risk factors for the development of cancer (Table 1). Overall, the average one year weight loss was 27% among patients undergoing bariatric surgery vs 1% in matched non-surgical patients.

In Cox proportional hazards models that included both surgery status and percent weight loss as predictors of cancer incidence, estimated percent weight loss at one year was significantly associated with a reduced risk of any cancer in the unadjusted model (HR 0.876, 95% CI 0.812–0.946, $p \le 0.001$ for every 10% weight loss) and in the model adjusted for other covariates (HR 0.897, 95% CI 0.832–0.968, p=0.005 for every 10% weight loss) while bariatric surgery was not a significant independent predictor in unadjusted or adjusted models (Table 2).

Kaplan Meier curves show that the unadjusted rates of incident cancer differed for patients having bariatric surgery by the amount of weight that was lost at 1 year (Figure 1). Those that lost the greatest amount of weight had the fewest cancers.

Next models for obesity-associated and non-obesity associated cancers were examined separately, while including both surgical and non-surgical patients in the same model. For non-obesity associated cancers, estimated percent weight loss at one year was associated with a reduced risk of cancer in both simple and adjusted Cox models, while bariatric surgery was not. For obesity associated cancers in unadjusted models we found no significant association between weight loss and cancer. In the adjusted models, bariatric surgery was associated with a reduced risk of cancer when controlling for weight loss, while estimated percent weight loss at one year was not significantly associated with a reduction in cancer risk.

The weight change during the study period was significantly different between patients who developed cancer and those who did not for patients who had bariatric surgery. Among surgical patients, estimated weight loss at one year was less for those who developed cancer compared to those who did not (24.4% vs 27.4%; $p \le 0.001$). Whereas among the nonsurgical matches, no differences in 1 year estimated weight loss were observed between those who developed cancer and those who did not (0.10% vs 0.8%; p=0.47)

We also investigated the effect of weight loss separately in those who underwent bariatric surgery and those who did not. In patients who had bariatric surgery, estimated percent weight loss at one year was significantly associated with a reduced risk of any type of cancer in both unadjusted (HR 0.797, 95% CI 0.712–0.891, p≤0.001 for a 10% weight loss) and adjusted (HR 0.859, 95% CI 0.764–0.966, p=0.01 for a 10% weight loss) Cox models (Table 3). For obesity associated cancers, estimated percent weight loss at one year was significantly associated with a reduced risk of cancer in unadjusted (HR 0.831, 95% CI 0.706–0.980, p=0.03 for a 10% weight loss) but not in adjusted (HR 0.883, 95% CI 0.743–1.050, p=0.16 for a 10% weight loss) Cox models. For cancers not associated with obesity, estimated percent weight loss at one year was significantly associated with a reduced risk of cancer in both unadjusted (HR 0.765, 95% CI 0.656–0.892, p≤0.001 for a 10% weight loss) and adjusted (HR 0.839, 95% CI 0.717–0.983, p=0.03 for a 10% weight loss) Cox models. For the matched nonsurgical patients, estimated percent weight loss at one year did not significantly predict cancer.

Discussion

In our current study we find that cancer risk after bariatric surgery appears to be closely associated with the amount of weight loss achieved at one year. In adjusted models, the association between bariatric surgery and cancer risk was explained by weight loss and was not independently associated with surgery. In the group having bariatric surgery, weight loss reduced the risk of cancer overall and also among the subset of non-obesity associated cancers.

While previous work has shown that bariatric surgery reduces the risk of obesity associated cancers[16–20], we did not find statistically significant evidence in this study that the reduction of obesity associated cancers among bariatric surgery patients was associated with weight loss.

For patients having bariatric surgery, for each 10% of weight loss there was an 14% reduction in cancer risk. Thus, for the average bariatric patient who loses 27% of their weight at 1 year, the reduction in cancer risk is 34% using the adjusted results (46% with the unadjusted results). Among obese matches who did not undergo bariatric surgery, estimated weight loss was small (1% at one year) and was not associated with a change in cancer risk.

Two other studies have examined the associated between weight loss after bariatric surgery and cancer risk. The first, a well matched prospective cohort study of more than 2,000 bariatric surgery cases, found no association between amount of weight loss and cancer risk using weight change during the first year following surgery[20]. Despite a mean follow-up of over 10 years, only 117 cancers occurred in the surgery group. The second study, a retrospective study of 2,943 patients having bariatric surgery, found that percent total weight loss at one year was significantly less in the group that developed cancer compared to the group that did not develop cancer (27.8% vs 31.2%)[24]. Over the mean follow-up of 3.8 years, 54 patients developed cancer.

We also found some seemingly paradoxical results. For obesity associated cancers, weight loss was not associated with lower cancer risk in our models that included both surgical patients and non-surgical patients. This may be because surgery was included in the models.

If surgery is removed from the model, percent weight loss is highly associated with cancer risk but it is impossible to tell with this sample size if it is weight loss or surgery that is the important predictor of obesity associated cancer. Since the risk of obesity associated cancers was decreased compared to matched nonsurgical patients, it suggests that there are either other mechanisms beyond weight loss that are more important in mediating the risk or that even small amounts of weight loss are enough to mitigate the risk of obesity associated cancer. More research is needed to determine the mechanism for obesity associated cancers.

For non-obesity associated cancers, we found a significant association with weight loss. This suggests that the list of obesity associated cancers may need to be expanded[23] and the mechanisms driving these associations may need to be further elucidated.

There are several limitations to the current study. Unmeasured differences may exist between the bariatric surgery patients and the matched nonsurgical patients. For example, bariatric surgery may have motivated patients to make lifestyle changes that are associated with a reduced risk of cancer. The amount of weight loss in the nonsurgical patients was very different from that in the bariatric surgery patients. This made interpretation of the models including weight loss and surgery difficult as there was collinearity between weight loss and surgery. We were unable to conduct sub-analyses for each specific bariatric procedure due to small sample sizes for the non-gastric bypass procedures. This is a limitation as the different bariatric procedures may have differing effects on cancer risk.

Conclusion

In this large, multisite cohort of patients with severe obesity, weight loss after bariatric surgery was associated with a lower risk of incident cancer. There was no apparent effect of bariatric surgery on cancer risk that was independent of weight loss. This provides further evidence to support the idea that substantial weight loss may reduce cancer risk.

Acknowledgments

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What is known

Bariatric surgery has been shown to reduce the risk of cancer. It is unknown if the reduction in risk is related to weight loss or other mechanisms.

What does the study add

Weight loss after bariatric surgery was associated with a lower risk of incident cancer. There was no apparent independent effect of the bariatric surgery itself on cancer risk that was independent of weight loss.

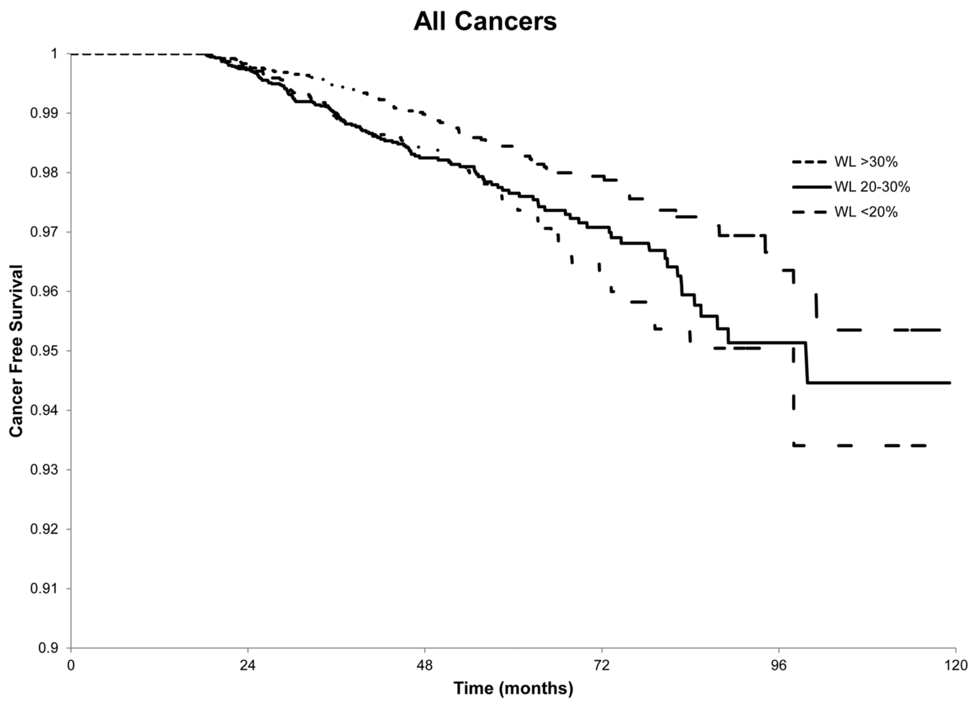

Figure 1.

Kaplan-Meier Estimated Cancer-Free Survival for All Cancers in Patients who underwent Bariatric Surgery by Percent Weight Loss (WL) at One Year. There were 7,295 surgery patients in the group that lost > 30% of their weight, 7,224 surgery patients in the group that lost 20–30% of their weight and 3,836 surgery patients who lost less than 20% of their weight at 1 year.

Table 1

Baseline Characteristics of Bariatric Surgical Patients and Matched Non-Surgical Patients

	Surgical Patients (n=18355)	Matched Non-Surgical Patients (n=40524)	Standardized Difference
Female (%)	82.1	80.8	a
Age (yrs), mean (SD)	45.5 (11.0)	46.3 (11.1)	0.06
Body Mass Index, mean (SD), kg/m2	44.7 (6.7)	44.5 (6.4)	0.04
Follow-up, mean (SD), months	50.8 (21.1)	48.6 (21.5)	0.1
% wt loss, 12 month	27.3 (9.3)	1.0 (6.6)	3.5
Race/ethnicity			
Non-hispanic white (%)	48.6	42.8	
Hispanic (%)	30.6	32.9	
African-American (%)	16.6	16.9	
Asian (%)	1.5	2.4	
Other (%)	2.9	5.1	
Site (%)			
Group Health Cooperative	4.8	5.1	
Kaiser Permanente Southern Cal.	59.4	59.4	
Kaiser Permanente Nouthern Cal.	27.1	26.2	
Kaiser Permanente Northwest	2	2.2	
Kaiser Permanente Colorado	6.8	7.2	
Clinical Characteristics[b]			
Diabetes (%)	35.4	40.5	0.1
% of Patients with Diabetes on Insulin	31.2	30.6	0.01
% of Patients with Diabetes on Metformin	60	63.5	0.07
Hypertension (%)	61.5	66.1	0.09
Hyperlipidemia (%)	44.4	42.4	0.04
% of Patients with Hyperlipidemia on Statins	72.4	83.1	0.27
Coronary Artery Disease (%)	2.2	2.5	0.02
Smoker, ever (%)[c]	32.3	27.1	0.11
Nonalcoholic steatohepatitis (%)	2.9	1.5	0.1
Alcohol Abuse (%)	1.4	2.2	0.06
Peripheral Vascular Disease (%)	1.1	2	0.07
Cerebral Vascular Disease (%)	0.8	1.3	0.05
Use of Hormone Replacement Therapy			
Estrogen Only (% of women)	3.3	2.4	
Progesterone Only (% of women)	2.8	2.7	
Combination (% of women)	1.9	1.3	
Elixhauser, mean (SD)	1.8 (1.6)	1.8 (1.5)	0.05
Mammogram (%)	20.4	24.9	0.11

	Surgical Patients (n=18355)	Matched Non-Surgical Patients (n=40524)	Standardized Difference
Bariatric Procedure Type (n,%)			
Gastric Bypass	11120 (61%)		
Sleeve Gastrectomy	5120 (28%)		
Laproscopic adjustable band	1023 (6%)		
Other[d]	14 (<1%)		
Indeterminate[e]	1078 (6%)		

[a]Cases and Controls matched exactly

[b]All clinical conditions were identified in the year prior to the index date

[c]Smoking was only identified using ICD-9 codes

[d]Other includes biliopancreatic diversion and vertical gastric banding

[e]Indeterminate includes procedures for which more than one procedure type was coded for on the same day

Table 2

Hazard Ratios for the Risk of Cancer by Type of Cancer[a]

	Unadjusted			Adjusted[b]		
All Cancers	**Hazard Ratio**	**95% Confidence Interval**	**p-value**	**Hazard Ratio**	**95%Confidence Interval**	**p-value**
Bariatric Surgery	0.987	0.774–1.258	0.92	0.931	.731–1.186	0.56
10% Weight Loss	0.876	0.812–0.946	<.001	0.897	.832–.968	0.005
Obesity Associated Cancers						
Bariatric Surgery	0.729	0.526–1.012	0.06	0.716	0.515–0.994	0.046
10% Weight Loss	0.908	0.821–1.004	0.06	0.927	0.838–1.026	0.14
Non-Obesity Associated Cancers						
Bariatric Surgery	1.04	0.981–2.019	0.06	1.261	0.883–1.801	0.2
10% Weight Loss	0.84	0.748–0.943	0.003	0.864	0.771–0.968	0.01

[a]Models include both bariatric surgical patients and matched non-surgical patients

[b]Models adjusted for race, diabetes, hyperlipidemia, hypertension, coronary artery disease, peripheral vascular disease, nonalcoholic steatohepatitis, a history of smoking, alcohol use, and use of hormone replacement therapy.

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Table 3

Hazard Ratios for the Risk of Cancer for Each Group

		Unadjusted			Adjusted[c]		
	Number of Cancers	Hazard Ratio	95% Confidence Interval	p-value	Hazard Ratio	95% Confidence Interval	p-value
Bariatric Surgery Patients[a]							
All Cancers	305	0.797	0.712–0.891	<.001	0.859	0.764–0.966	0.01
Obesity Associated Cancers	145	0.831	0.706–0.980	0.03	0.883	0.743–1.050	0.16
Non-Obesity Associated Cancers	161	0.765	0.656–0.892	<.001	0.839	0.717–0.983	0.03
Matched Non-Surgical Patients[b]							
All Cancers	891	0.945	0.855–1.046	0.28	0.941	0.848–1.043	0.25
Obesity Associated Cancers	523	0.956	0.838–1.09	0.5	0.938	0.819–1.074	0.36
Non-Obesity Associated Cancers	368	0.931	0.795–1.091	0.38	0.944	0.804–1.108	0.48

[a]Models include only bariatric surgical patients

[b]Models include only matched non-surgical patients

[c]Models adjusted for study site, age, sex, BMI, race, diabetes, hyperlipidemia, hypertension, coronary artery disease, peripheral vascular disease, nonalcoholic steatohepatitis, a history of smoking, alcohol use, and use of hormone replacement therapy.