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

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

Methods: A retrospective matched cohort study of patients undergoing bariatric surgery was conducted 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 nonsurgical 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 during up to 10 years of follow-up.

Results: The study identified 1,196 cases of incident cancer. The average 1-year postsurgical weight loss was 27% among patients undergoing bariatric surgery versus 1% in matched nonsurgical patients. Percent weight loss at 1 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.

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.

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% to 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 that are associated with obesity and lead to a rise in cancer risk are potentially modifiable by weight loss. After weight loss by either diet or exercise, adipose-tissue gene expression changes at 6 months for both steroid-hormone metabolism and insulin-like growth factor 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 kg 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-kg 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, the Northwest [Oregon], Colorado, and Washington [formerly Group Health Cooperative]). The cohort included individuals with obesity 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 review to the KP Colorado Institutional Review Board.

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 years at time of surgery (152); presurgical history of cancer (2,492); and without BMI measurement (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 1 year; BMI; and Elixhauser comorbidity index (22). Nonsurgical patients were provisionally matched to multiple surgical patients based upon region, sex, and birthdate within 1 year. Potential matches were then excluded if they had a prior cancer or if their BMI was not within 5% of the surgical patient’s. 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 three nonsurgical 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 nonsurgical 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; 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 on each side of the 12-month follow-up.

Estimated percent weight loss was calculated for 1 year after surgery for bariatric surgery patients or 1 year after the index date for nonsurgical 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 [post-menopausal], 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 (23). All other cancers were considered not associated with obesity.

To characterize the study sample, we calculated means, medians, and frequencies for variables used as covariates in the Cox proportional hazards models as well as other factors of interest. 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 nonobesity-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 nonsurgery patients employed the additional covariates of those factors that had been used in the matching.

Because percent weight loss and bariatric surgery were highly collinear, hazard ratios (HR) 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 nonparsimonious 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-related and non-

TABLE 1 Baseline characteristics of bariatric surgical patients and matched nonsurgical patients

|                                | Surgical patients | Matched nonsurgical patients | Standardized difference |
|--------------------------------|-------------------|------------------------------|-------------------------|
|                                | (n = 18,355)      | (n = 40,524)                 |                         |
| Female (%)                     | 82.1              | 80.8                         | a                       |
| Age (y), mean (SD)             | 45.5 (11.0)       | 46.3 (11.1)                  | 0.06                    |
| BMI (kg/m²), mean (SD)         | 44.7 (6.7)        | 44.5 (6.4)                   | 0.04                    |
| Follow-up (mo), mean (SD)      | 50.8 (21.1)       | 48.6 (21.5)                  | 0.1                     |
| % Weight loss, 12 months       | 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 California | 59.4          | 59.4                         |                         |
| Kaiser Permanente Northern California | 27.1          | 26.2                         |                         |
| Kaiser Permanente Northwest    | 2                 | 2.2                          |                         |
| Kaiser Permanente Colorado     | 6.8               | 7.2                          |                         |
| Clinical characteristicsb      |                   |                              |                         |
| 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                    |
| Bariatric procedure type, n (%)|                   |                              |                         |
| Gastric bypass                 | 11,120 (61%)      |                             |                         |
| Sleeve gastrectomy             | 5,120 (28%)       |                             |                         |
| Laparoscopic adjustable band   | 1,023 (6%)        |                             |                         |
| Otherd                         | 14 (<1%)          |                             |                         |
| Indeterminatee                 | 1,078 (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.
obesity-related cancers. Within this set of models, we tested the proportional hazards assumption by adding interactions between time and each 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 \( P \leq 0.05 \), unadjusted for multiple tests, and all analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

The final matched cohort had 18,355 bariatric surgery patients and 40,524 nonsurgical 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 1-year weight loss was 27% among patients undergoing bariatric surgery versus 1% in matched nonsurgical 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 1 year was significantly associated with a reduced risk of any cancer in the unadjusted model (HR 0.876, 95% confidence interval [CI]: 0.812-0.946, \( P < 0.001 \) 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 who lost the greatest amount of weight had the fewest cancers.

Next, models for obesity-associated and nonobesity-associated cancers were examined separately, while including both surgical and nonsurgical patients in the same model. For nonobesity-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 1 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

| TABLE 2 Hazard ratios (HR) for the risk of cancer by type of cancer\(^a\) |
|-----------------------------|-----------------------------|-----------------------------|
|                             | Unadjusted                 | Adjusted\(^b\)               |
|                             | HR 95% CI  | \( P \) value | HR 95% CI  | \( P \) value |
| All cancers                 |             |               |             |               |
| Bariatric surgery           | 0.987      | 0.774-1.258  | 0.92       | 0.931        | 0.731-1.186  | 0.56         |
| 10% Weight loss             | 0.876      | 0.812-0.946  | <0.001     | 0.897        | 0.832-0.968  | 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         |
| Nonobesity-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 nonsurgical 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 (HR) for the risk of cancer for each group

| Number of cancers | Unadjusted | 95% CI | P value | Adjusted |
|-------------------|------------|--------|---------|----------|
|                   | HR         |        |         | HR       |         |
| Bariatric patients |            |        |         |          |         |
| All cancers       | 0.797      | 0.712-0.891 | <0.001  | 0.859    | 0.764-0.966 | 0.01 |
| Obesity-associated cancers | 0.831 | 0.706-0.980 | 0.03 | 0.883    | 0.743-1.050 | 0.16 |
| Nonobesity-associated cancers | 0.765 | 0.656-0.892 | <0.001  | 0.839    | 0.717-0.983 | 0.03 |
| Matched nonsurgical patients |         |        |         |          |         |
| All cancers       | 0.945      | 0.855-1.046 | 0.28 | 0.941    | 0.848-1.043 | 0.25 |
| Obesity-associated cancers | 0.956 | 0.838-1.090 | 0.5 | 0.938    | 0.819-1.074 | 0.36 |
| Nonobesity-associated cancers | 0.931 | 0.795-1.091 | 0.38 | 0.944    | 0.804-1.108 | 0.48 |

*aModels include only bariatric surgical patients.
*bModels include only matched nonsurgical patients.
$cModels 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.

for patients who had bariatric surgery. Among surgical patients, estimated weight loss at 1 year was less for those who developed cancer compared to those who did not (24.4% vs. 27.4%; \( P \leq 0.001 \)), 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 1 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, \( P \leq 0.001 \)) 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. For obesity-associated cancers, estimated percent weight loss at 1 year was significantly associated with a reduced risk of cancer in both unadjusted (HR 0.839, 95% CI: 0.717-0.983, \( P = 0.03 \)) for a 10% weight loss) Cox models. For cancers not associated with obesity, estimated percent weight loss at 1 year was significantly associated with a reduced risk of cancer in both unadjusted (HR 0.765, 95% CI: 0.656-0.892, \( P \leq 0.001 \)) 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 1 year did not significantly predict cancer.

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 a 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 obesity matches who did not undergo bariatric surgery, estimated weight loss was small (1% at 1 year) and was not associated with a change in cancer risk.

Two other studies have examined the association 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 1 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 nonsurgical 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. Because 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 nonobesity-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.

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