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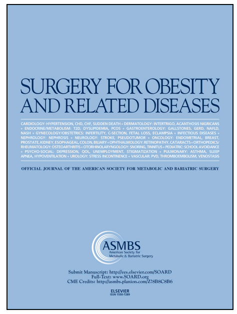

Development of Cancer after Bariatric Surgery

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Short title: Development of Cancer after Bariatric Surgery

Abstract

Setting: Although bariatric surgery has been associated with a reduction in risk of obesity-related cancer, data on the effect of bariatric interventions on other cancers is limited.

Objectives: This study aimed to examine the relationship between bariatric interventions and the incidence of various cancers following bariatric surgery.

Methods: The New York Statewide Planning and Research Cooperative System database was used to identify all adult patients diagnosed with obesity between 2006 and 2012 and patients who underwent bariatric procedures without pre-existing cancer diagnosis, alcohol or tobacco use. Subsequent cancer diagnoses were captured up to 2016. Multivariable proportional sub-distribution hazard regression analysis was performed to compare the risk of having cancer among obese patients with and without bariatric interventions.

Results: We identified 71,000 patients who underwent bariatric surgery and 323,197 patients without a bariatric intervention. Patients undergoing bariatric surgery were less likely to develop both obesity-related cancer (hazard ratio (HR) 0.91; 95% CI, 0.85-0.98; $p=0.013$) and other cancers (HR 0.81; 95% CI, 0.74-0.89; $p<0.0001$). Patients undergoing Roux-en-Y gastric bypass had a lower risk of developing cancers that are considered non-obesity related (HR 0.59; 95% CI, 0.42-0.83; $p=0.0029$) compared to laparoscopic sleeve gastrectomy.

Conclusions: Bariatric surgery is associated with a decreased risk of obesity-related cancers. More significantly, we demonstrated the relationship between bariatric surgery and the reduction of the risk of some previously designated non-obesity related cancers, as well. Reclassification of non-obesity related cancers and expansion of bariatric indications for reducing the risk of cancer may be warranted.

Keywords: Bariatric surgery; obesity-related cancer; non-obesity related cancer; obesity; cancer

INTRODUCTION

Obesity has emerged as an epidemic in America [1]; it was estimated that the mean body weight of the average American has increased by nearly 10% in the two decades since 1980, after adjusting for age and height [1]. At the same time, the prevalence of clinical obesity has almost doubled [1]. There is no significant gender difference in the prevalence of obesity [2]. The associated comorbidities such as hypertension, type 2 diabetes (T2D), dyslipidemia, gall bladder disease, osteoarthritis, etc. has been demonstrated in numerous studies [3-5]. The International Agency for Research on Cancer (IARC) has also designated 14 types of cancer as obesity-related, such as esophageal, gallbladder, liver, pancreatic, colorectal, thyroid, renal, prostate, ovarian, endometrial and postmenopausal breast cancer in females [6-9]. It is estimated that obesity alone accounts for 20% of all cancer causes [6]. Obesity is also found to be a cause in 14% of cancer deaths in males and up to 20% of cancer deaths in females [7].

Bariatric surgery has become a popular treatment option for morbidly obese patients due to its effectiveness, significant weight reduction and reduction in developing comorbidities such as cardiovascular, endocrine and infectious disorders [10]. However, studies evaluating the relationship between bariatric surgery and risk reduction of different types of cancer are limited. Previous studies have demonstrated that insurance status affects cancer-related health care quality and outcomes [11, 12], suggesting the existence of health care disparity. Understanding the impact of insurance on cancer incidence is particularly relevant given the need to expand health insurance in the US. The purpose of this study was to determine if bariatric surgery is associated with a lower incidence of obesity-related and non-obesity related cancer compared with a matched cohort of obese patients with the same age, gender, race and ethnicity.

METHODS

We conducted a retrospective analysis study using data from the New York Statewide Planning and Research Cooperative System (SPARCS) administrative database. SPARCS is a longitudinal comprehensive data reporting system. Patient level data such as patient characteristics, diagnoses and treatments, and services provided can be collected. Data covering January 1st, 2006 through December 31st, 2012 was used to identify all patients who had obesity diagnosis. The Institution Review Board of Stony Brook University Hospital approved the study protocol.

International Classification of Diseases, ninth (ICD-9) revision codes for obesity (278.00, 278.01, 278.02, 278.03) were used to identify obese adult patients. This included all adult patients with body mass index (BMI) at or above 30. Exclusion criteria included age < 18 years, missing identifiers, missing gender information, and duplicate records. Two groups of patients – those who underwent bariatric surgery and those who did not were defined using records with obesity diagnosis. Current Procedural Terminology (CPT), ICD-9 codes for laparoscopic bariatric surgery procedures were then used to identify bariatric surgery patients who underwent revision bariatric surgery (diagnosis of V45.86), Laparoscopic Sleeve Gastrectomy (LSG) (43.82, 43.89 and 43775 with primary diagnosis of 278.00-02), Roux-en-Y Gastric Bypass (RYGB) (44.38, 43644 and 43645 with primary diagnosis of 278.00-02) and Laparoscopic Adjustable Gastric Banding (LAGB) (44.95 and 43770 with primary diagnosis of 278.00-02). Patients with at least one primary or revisional bariatric surgery were included in the surgical group. Patients from both the surgical and non-surgical group were followed starting from their earliest records with an obesity diagnosis code during the study period. Patients having any benign or malignant neoplasm diagnosis, tobacco use and alcohol abuse, identified by ICD-9 codes, in their earliest records or at the time of bariatric surgery were also excluded (Figure 1). Subsequent cancer diagnoses, identified by ICD-9 and ICD-10 codes, were captured up to 2016 (See Appendix A for specific diagnosis codes used). To investigate gender-specific difference between the surgical and non-surgical groups, gender-specific cancers such as prostate cancer (ICD-9 code: 185) were considered as separate groups and were not included in the category of obesity-related cancer even though they were designated as such according to IARC. Otherwise, cancer diagnoses were considered "obesity-related" or "non-obesity related" following IARC classification.

All bariatric surgery patients were matched to patients who did not have bariatric surgery with identical race and ethnicity, gender and age for our analysis cohort. Chi-square tests with exact P-values based on Monte Carlo simulation were utilized to compare patients' characteristics between bariatric surgery and non-bariatric surgery patients, as well as those between bariatric surgery patients with different bariatric surgery types. Univariate proportional sub-distribution hazards models (Fine-Gray models) were utilized to examine the marginal association between potential factors (surgical or non-surgical groups, patients' characteristics, complications, comorbidities) and the risk of obesity-related, non-obesity related and any type of cancer. Fine-Gray models were utilized since death was treated as a competing risk event for cancer development. Patients' group and other factors related to each outcome that were significant (p-value<0.05) based on univariate analysis were further considered in multivariable Fine-Gray models. A separate subgroup analysis was performed among primary bariatric surgery patients to compare obesity-related, non-obesity related and any types of cancer risks across the three bariatric surgery types. In Fine-Gray models, a hazard ratio (HR) >1 indicated higher risk of cancer development, while an HR <1 indicated lower risk. Statistical analysis was performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) and significance level was set at 0.05.

RESULTS

<u>Patients in the surgical and non-surgical groups</u>

We identified 765,500 obese patients- 71,000 of them underwent bariatric surgery and 694,500 of them did not. After matching for race and ethnicity, age and gender, 323,197 records from the non-surgical group were kept (See Appendix B for patient characteristics in the surgical and non-surgical groups before and after matching). Thus, in total, we used 394,197 records in analyses. Bariatric surgery patients were matched to patients who did not have bariatric surgery in an approximately 1:5 ratio based on the available number of records from the non-surgical group. The number of patients collected per year between 2006 and 2012 is displayed in Appendix C. The number of in-hospital deaths in surgical and non-surgical groups during the follow up period is illustrated in Appendix D. Over 76% of the patients were female, based on surgical trends and the matching algorithm (See Appendix E for patient characteristics in the surgical and non-surgical groups). 1,448 (2.04%) surgical patients developed cancer compared with 7,695 (2.38%) non-surgical patients.

Cancer incidence in surgical and non-surgical groups

The incidence of patients developing obesity-related cancer was 1.31% and 1.45% for the surgical and non-surgical groups respectively. The incidence for non-obesity related cancer was 0.80% and 1.01% for the surgical and non-surgical groups respectively (Table 1). The estimated cumulative incidence of any types of cancers for the surgical group was 0.3% (95% CI, 0.3%-0.3%) at 1 year, 2% (95% CI, 1.8%-2.1%) at 5 years and 5.3% (95% CI, 4.8%-5.7%) at 10 years, while that for the non-surgical group was 0.6% (95% CI, 0.6%- 0.6%), 2.3% (95% CI, 2.3%- 2.4%) and 6.0% (95% CI, 5.8%-6.2%) respectively (Figure 2). The estimated cumulative incidence of any type of cancer, obesity-related cancer and non-obesity related cancer in the surgical and non-surgical groups with respect to gender is illustrated in Appendix F.

Comparison of the risk of cancer development in surgical and non-surgical groups

Bariatric surgery patients were less likely to develop any type of cancer (HR 0.87; 95% CI, 0.82-0.92; p<0.0001), obesity related (HR 0.91; 95% CI, 0.85-0.98; p=0.013) and non-obesity related cancer (HR 0.81; 95% CI, 0.74-0.89; p<0.0001) than patients who did not have bariatric surgery. Among obesity-related cancer, the reduction of liver and pancreatic cancer incidence was the most strongly associated with bariatric interventions. Among non-obesity-related cancer, the reduction of bronchus and lung cancer incidence was the most strongly associated with bariatric interventions (Table 1).

For male specific cancer, there was no significant difference between bariatric surgery and non-bariatric surgery patients in the development of prostate cancer (HR 1.15; 95% CI, 0.98-1.35; p=0.0931) (See Appendix G for estimated hazard ratios).

Cancer incidence with different bariatric procedures

The incidence of developing post-operative cancer within each bariatric procedural group are reported in Table 2. 1.29% of patients undergoing sleeve gastrectomy, 1.65% of gastric bypass patients and 2.39% of gastric banding patients developed any type of cancer. This was also the case for obesity-related cancer (LSG: 0.76%, RYGB: 1.07%, LAGB: 1.45%), non-obesity related cancer (LSG: 0.56%, RYGB: 0.64%, LAGB: 1.01%) and male specific cancer (LSG: 0.45%, RYGB: 0.58%, LAGB: 0.87%). Among obesity-related cancer, the reduction in the incidence of gallbladder and extrahepatic bile duct cancer was the most strongly associated with laparoscopic sleeve gastrectomy. The reduction of melanoma incidence was the most strongly associated with laparoscopic sleeve gastrectomy among all non-obesity-related cancer.

Comparison of the risk of cancer development in different bariatric surgeries

Among the three different types of bariatric surgeries- laparoscopic sleeve gastrectomy, Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding, there was no significant difference between the three in terms of the risk of postoperative obesity-related cancer (Table 3) and male specific cancer. However, patients undergoing Roux-en-Y gastric bypass had a lower risk of developing non-obesity related cancer (HR 0.59; 95% CI, 0.42-0.83; p=0.0029) (Table 4) and any type of cancer (HR 0.69; 95% CI, 0.55-0.86; p=0.0002) than laparoscopic sleeve gastrectomy. Patients undergoing Roux-en-Y gastric bypass also had a lower risk of developing non-obesity related cancer (HR 0.78; 95% CI, 0.63-0.95; p=0.0029) and any type of cancer than laparoscopic adjustable gastric banding (HR 0.80; 95% CI, 0.71-0.92; p=0.0002). There were no significant differences between laparoscopic adjustable gastric banding and laparoscopic sleeve gastrectomy in terms of the risk of postoperative non-obesity related cancer (HR 0.76; 95% CI, 0.55-1.06; p=0.0029) and any type of cancer (HR 0.86; 95% CI, 0.69-1.07; p=0.0002). Within the surgical group, patients with commercial insurance had a lower risk of developing obesity-related (HR 0.67; 95% CI, 0.53-0.84; p=0.0057), non-obesity-related cancer (HR 0.71; 95% CI, 0.54-0.93; p=0.098) and any type of cancer (HR 0.64; 95% CI, 0.54-0.76; p<0.0001) compared to patients with Medicare.

DISCUSSION

Obesity is associated with multiple comorbidities including coronary artery disease and vascular disorder, hypertension [13], T2D [14], and respiratory conditions [15, 16]. It is also known to be a risk factor for developing many different types of cancer [6-9]. Although several previous studies demonstrated that bariatric surgery decreases the risk of obesity-related cancer [17-21], this is the first study to specifically examine the efficacy of different types of bariatric interventions on reducing the risk of cancer, in addition to investigating the effect of bariatric surgery on obesity-related, non-obesity related and gender specific cancer.

Bariatric surgery has been shown to be associated with reduced risk of obesity-related cancer [17-21]. The International Agency for Research on Cancer (IARC) designated obesity-related cancers include hepatocellular carcinoma, exocrine pancreatic, gallbladder, cholangiocarcinoma, colorectal, renal, adenocarcinoma of the esophagus and gastric cardia, prostate, postmenopausal breast, endometrial, ovarian, thyroid cancer and multiple myeloma [22-25]. In an observational 2-cohort study by Christou, there was significant and sustained weight loss as well as clinically significant reductions in the incidence of breast, colorectal and pancreatic cancers following bariatric surgery [19]. The risk of obesity-related cancer after Roux-en-Y gastric bypass is lowered with a hazard ratio of 0.62 (95% CI, 0.49-0.78; $P<0.0001$) [17]. However, the risk reduction of colorectal cancer after bariatric surgery does not appear to be so clear-cut. In a systemic review by Afshar et al., bariatric surgery is associated with a 27% lower colorectal cancer risk [26]. On the other hand, increased standardized incidence ratio of colorectal cancer in bariatric surgery patients with longer follow-up was observed in a retrospective cohort study by Derogar et al.; however, a similar pattern was not observed in obese patients without surgery [27]. Our study appears to agree with the former, showing a lower incidence of colorectal cancer in bariatric surgery patients when compared to non-surgical patients ($p=0.0043$).

Bariatric surgery also appears to reduce the risk of cancers not designated as obesity-related per IARC. A recent publication by Schauer et al. demonstrated that patients undergoing bariatric surgery had a 33% lower hazard risk of developing any type of cancer (HR 0.67; 95% CI, 0.6, 0.74; $p<0.001$) when compared to matched obese patients who did not undergo bariatric surgery [20]. Schauer also demonstrated the relationship between bariatric surgery and risk reduction in developing subsequent cancer is stronger for obesity-related cancer than non-obesity related cancer [20]. In addition to obesity-associated cancers designated by IARC, our study also evaluated non-obesity related cancers. We strikingly noted the decrease in the risk of non-obesity related cancer is more strongly associated with bariatric surgery than obesity-related cancer. We propose that previously designated non-obesity related cancers may in fact be obesity-related. This is supported by recent studies that have demonstrated an association between bariatric surgery and a reduced risk of melanoma and skin cancer in general [28], both of which were not previously classified as obesity-related cancers.

Various mechanisms have been proposed linking obesity to cancer. Chronic hyperinsulinemia of obesity exposes tissue to tumorigenic effects of insulin receptors found in (pre)neoplastic cells [29, 30]. Adiposity also influences the synthesis and increased bioavailability of estrogen, androgens, and progesterone, each of which has been linked to cancers through epidemiological studies [29, 30]. Chronic inflammation, which has been associated with obesity, is another proposed mechanism. Two pro-inflammatory pathways, c-Jun NH2-terminal kinase (JNK) and IκB kinase-β (IKK-β), are increased in adiposity and may be part of the link between adipose tissue, inflammation, and immune cells that play a role in cancer formation [30]. Chronic inflammation also contributes to the development of insulin resistance – a previous proposed tumorigenic mechanism [29, 31, 32].

The risk of gender specific cancer is also found to be reduced in multiple studies. In an observational cohort study by Christou, bariatric surgery patients had lower incidence of postoperative endometrial and breast cancers when compared to those who did not have bariatric surgery [18]. Specifically, there is a 71% reduction in the risk of developing uterine malignancy for obese women who had bariatric surgery compared to those who did not [33]. A meta-analysis demonstrated similar findings, where the relative risk of endometrial cancer is 0.4 for bariatric patients compared to obese control patients [34]. A decreased risk of prostate cancer was noted in bariatric patients during follow-up, however, it was not statistically significant [35]. Our study aligned with these previous results; the risk of female-specific cancer was reduced after bariatric surgery [36] but there was no significant difference in the risk reduction of prostate cancer in both groups. Despite both arms of our study having increased female patients due to matching algorithms, we still had 15,219 and 76,095 male patients in the surgical and non-surgical groups respectively. Since most gender specific cancers are also obesity-related, it is expected to show similar pattern as those found in obesity-related cancer. In addition to gender specific effects, our study showed that patients with commercial insurance appeared to have lower risk of developing cancer when compared to patients with Medicare. This might be attributed to enhanced screening in commercial insurance holders. Further study is essential to identify the reason behind the healthcare disparity associated with insurance status.

A limited number of studies compared the different types of bariatric interventions in decreasing the risk of cancer. The underlying mechanisms of bariatric intervention on cancer risk reduction may involve both weight-dependent and weight-independent effects. From other published studies it is well known that with any bariatric procedure, on average, sustained weight loss is achieved through caloric restriction [37]. Other possible mechanisms include improvement of insulin resistance and glucose metabolism, which attenuate metabolic syndrome, decreased inflammation and oxidative stress, improved regulation of sex hormones, gastrointestinal hormone ghrelin, improved cellular energy homeostasis and increased energetic efficiency [38]. Our study showed that Roux-en-Y gastric bypass appears to be a better approach compared to laparoscopic adjustable gastric banding and laparoscopic sleeve gastrectomy in terms of cancer risk reduction. Patients undergoing Roux-en-Y gastric bypass has also been shown to have greater weight loss compared to laparoscopic adjustable gastric banding and laparoscopic sleeve gastrectomy [39]. Assuming the patient population of our study is similar to previous studies and follows average weight loss outcomes, the observation of lower cancer risk in patients undergoing Roux-en-Y gastric bypass may be attributed by the greater body weight loss achieved through Roux-en-Y gastric bypass [39]. However, it is also suggested that rectal mucosal changes may occur in relation to malabsorptive effects of Roux-en-Y gastric bypass, which can possibly increase the risk of colorectal cancer after surgery [27]. This implies that it is important to compare the effect of different types of bariatric interventions on the risk of post-surgical cancer occurrence.

The rigor of this retrospective study is limited by the use of administrative data. Clinical information such as BMI before and after bariatric surgery is not available. BMI is a significant variable that can affect the assessment of surgery outcomes. There appears to be some association between BMI and the risk of multiple cancers [40-42]. Therefore, preoperative and postoperative BMI is an important determinant of cancer risk. According to George et al., the use of the ICD-9 diagnosis code for obesity was shown to identify morbidly obese patients easily; many patients with morbid obesity had ICD-9 code for obesity, but not specifically as morbid obesity used in clinical databases [43].

Moreover, the effect of morbid obesity defined using ICD-9 codes and BMI on complications were similar [43]. This suggests that the use of ICD-9 codes to identify patients with obesity may be comparable to using BMI. However, the use of diagnosis codes limits the accuracy and severity of the diagnosis. Esophageal adenocarcinoma is associated with obesity; however, the use of diagnosis codes alone will detect both esophageal adenocarcinoma and esophageal squamous cell carcinoma but not specifically esophageal adenocarcinoma. Since there are many non-obesity related cancers, only certain non-obesity related cancers were investigated and included in this study, which may not be accurate to generalize. The use of administrative data also gives rise to the potential of miscoding. Selection bias can exist; patients who undergo bariatric procedures may have large variations in terms of lifestyle and different social factors, which cannot be accounted for in this study. However, the large sample size is the strength of our study. Since New York SPARCS database capture records across all participating hospitals within New York State, it is an ideal database to capture patients undergoing bariatric procedures. Patients each have unique identifiers and as such the true incidence of any cancer diagnosis managed at any hospital within the state can be captured, not limited to the hospital for the original bariatric procedure. Administrative data was also used for some other large cancer incidence studies [10, 18, 20]. Although the use of such a large population-based database is limited in terms of the clinical information, it is the only way to provide some insight into low count events, such as the development of cancer.

Since our study was observational and retrospective in nature, it is not a proof of a direct effect but rather allows for the novel demonstration of a possible relationship between bariatric surgery and reduced risk of subsequent cancer development. Bariatric surgery is not to be considered as a treatment for cancer, but rather a possible intervention to prevent development of cancer. This is especially important in certain cancer-prone populations, such as those who have a strong family history of cancer. Therefore, the argument for expanded coverage for bariatric surgery to include those who are overweight or obese and at an increased risk of cancer should be explored.

CONCLUSION

Our study confirms bariatric surgery is associated with a reduction in the risk of obesity-related cancers. More importantly, the evidence suggest bariatric surgery is also associated with a reduction in the risk of some previously designated non-obesity related cancers as well. This significant finding may warrant further investigation and possible reclassification of non-obesity related cancers to obesity-related. No significant association between bariatric surgery and male-specific cancer was noted. The present study also provides evidence supporting the expansion of bariatric surgery coverage to include overweight and obese patients who are at an increased risk of cancer.

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Table 1. Incidence of cancer development by surgical and non-surgical group

Table 2. Incidence of cancer development by primary bariatric surgery types

Table 3. Estimated hazard ratios of explanatory variables and their 95% confidence intervals for post-operative obesity-related cancer development based on a multivariable Fine-Gray model

Table 4. Estimated hazard ratios of explanatory variables and their 95% confidence intervals for post-operative non-obesity related cancer development based on a multivariable Fine-Gray model

Figure 1. Cohort consort for surgical and non-surgical controls

Figure 2. Cumulative incidence of obesity-related, non-obesity related and any types of cancer by patients' group

Table 1. Incidence of cancer development by surgical and non-surgical group

Cancer type	Total (N=394,197)	Non-surgical group (N=323,197)	Surgical group (N=71,000)	P-values*
Any type of cancer				
Any type of cancer	**9143 (2.32%)**	**7695 (2.38%)**	**1448 (2.04%)**	**<.0001**
Obesity related cancer				
Obesity related cancer	**5635 (1.43%)**	**4702 (1.45%)**	**933 (1.31%)**	**0.0042**
Malignant neoplasm of esophagus	223 (0.06%)	191 (0.06%)	32 (0.05%)	0.1547
Liver cancer	368 (0.09%)	324 (0.10%)	44 (0.06%)	0.0025
Pancreatic cancer	555 (0.14%)	481 (0.15%)	74 (0.10%)	0.0041
Cancer of the gallbladder, extrahepatic bile duct	172 (0.04%)	138 (0.04%)	34 (0.05%)	0.5489
Kidney cancer	1131 (0.29%)	937 (0.29%)	194 (0.27%)	0.4519
Colorectal cancer	1574 (0.40%)	1334 (0.41%)	240 (0.34%)	0.0043
Gastric cancer	136 (0.03%)	120 (0.04%)	16 (0.02%)	0.0580
Multiple Myeloma	386 (0.10%)	322 (0.10%)	64 (0.09%)	0.4642
Thyroid cancer	1418 (0.36%)	1140 (0.35%)	278 (0.39%)	0.1177
Non-obesity related cancer				
Non-obesity related cancer	**3830 (0.97%)**	**3265 (1.01%)**	**565 (0.80%)**	**<.0001**
Bronchus and Lung cancer	1561 (0.40%)	1362 (0.42%)	199 (0.28%)	<.0001
Heart cancer	5 (0.00%)	5 (0.00%)	0 (0.00%)	0.5874
Head and neck squamous cell carcinoma	149 (0.04%)	128 (0.04%)	21 (0.03%)	0.2133
Melanoma of skin	515 (0.13%)	410 (0.13%)	105 (0.15%)	0.1601
Non-Hodgkin Lymphoma	1031 (0.26%)	867 (0.27%)	164 (0.23%)	0.0783
Bladder Cancer	698 (0.18%)	603 (0.19%)	95 (0.13%)	0.0025

*: P-values were based on Chi-squared test with exact p-value from Monte Carlo simulation.

Table 2. Incidence of cancer development by primary bariatric surgery types

Cancer type	Total (N=58,127)	Gastric Band (N=19,777)	Gastric Bypass (N=30,358)	Sleeve Gastrectomy (N=7,992)	P-values*
Any type of cancer					
Any type of cancers	**1075 (1.85%)**	**472 (2.39%)**	**500 (1.65%)**	**103 (1.29%)**	**<.0001**
Obesity related cancer					
Obesity related cancer	**673 (1.16%)**	**287 (1.45%)**	**325 (1.07%)**	**61 (0.76%)**	**<.0001**
Malignant neoplasm of esophagus	21 (0.04%)	8 (0.04%)	10 (0.03%)	3 (0.04%)	0.9570
Liver cancer	31 (0.05%)	18 (0.09%)	11 (0.04%)	2 (0.03%)	0.0166
Pancreatic cancer	48 (0.08%)	19 (0.10%)	27 (0.09%)	2 (0.03%)	0.1465
Gallbladder, extrahepatic bile duct	25 (0.04%)	16 (0.08%)	9 (0.03%)	0 (0.00%)	0.0024
Kidney cancer	148 (0.25%)	65 (0.33%)	70 (0.23%)	13 (0.16%)	0.0221
Colorectal cancer	163 (0.28%)	70 (0.35%)	77 (0.25%)	16 (0.20%)	0.0399
Gastric cancer	11 (0.02%)	5 (0.03%)	5 (0.02%)	1 (0.01%)	0.7033
Multiple Myeloma	49 (0.08%)	22 (0.11%)	22 (0.07%)	5 (0.06%)	0.2649
Thyroid cancer	209 (0.36%)	81 (0.41%)	106 (0.35%)	22 (0.28%)	0.2169
Non-obesity related cancer					
Non-obesity related cancer	**438 (0.75%)**	**199 (1.01%)**	**194 (0.64%)**	**45 (0.56%)**	**<.0001**
Bronchus and Lung cancer	153 (0.26%)	72 (0.36%)	67 (0.22%)	14 (0.18%)	0.0023
Head and neck squamous cell carcinoma	18 (0.03%)	8 (0.04%)	8 (0.03%)	2 (0.03%)	0.7258
Melanoma of skin	83 (0.14%)	45 (0.23%)	32 (0.11%)	6 (0.08%)	0.0004
Non-Hodgkin Lymphoma	127 (0.22%)	57 (0.29%)	51 (0.17%)	19 (0.24%)	0.0175
Bladder Cancer	76 (0.13%)	26 (0.13%)	43 (0.14%)	7 (0.09%)	0.4924

*: P-values were based on Chi-squared test with exact p-value from Monte Carlo simulation.

Table 3. Estimated hazard ratios of explanatory variables and their 95% confidence intervals for post-operative obesity-related cancer development based on a multivariable Fine-Gray model

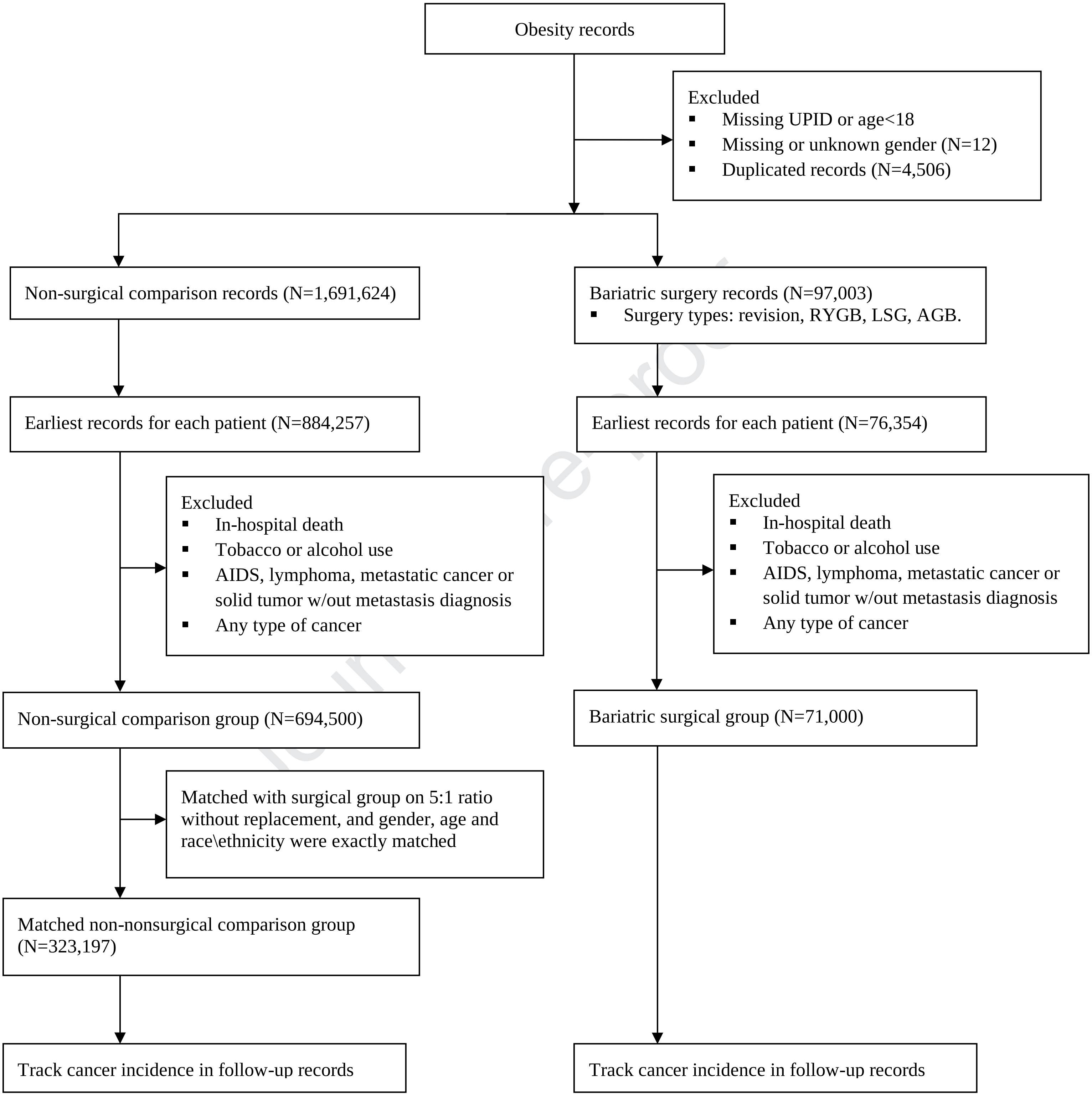
Variable	Level	Hazard Ratio with 95% Confidence Interval	P-value*
Surgery type	Gastric Band vs Gastric Bypass	1.203 (1.019, 1.419)	0.0556
	Gastric Band vs Sleeve Gastrectomy	0.957 (0.720, 1.273)	
	Gastric Bypass vs Sleeve Gastrectomy	0.796 (0.600, 1.056)	
Gender	Female vs Male	0.809 (0.680, 0.963)	0.0169
Age (continuous)	Unit=1 year	1.043 (1.034, 1.052)	<.0001
Race/ethnicity	Asian, non-Hispanic vs Black, non-Hispanic	3.134 (1.260, 7.796)	0.0807
	Asian, non-Hispanic vs Hispanic	2.866 (1.153, 7.125)	
	Asian, non-Hispanic vs Other	2.612 (1.059, 6.441)	
	Asian, non-Hispanic vs White, non-Hispanic	2.453 (1.017, 5.917)	
	Black, non-Hispanic vs Hispanic	0.914 (0.644, 1.298)	
	Black, non-Hispanic vs Other	0.833 (0.599, 1.159)	
	Black, non-Hispanic vs White, non-Hispanic	0.783 (0.598, 1.025)	
	Hispanic vs Other	0.912 (0.654, 1.271)	
	Hispanic vs White, non-Hispanic	0.856 (0.652, 1.124)	
	Other vs White, non-Hispanic	0.939 (0.741, 1.190)	
Insurance	Commercial vs Medicaid	0.878 (0.577, 1.335)	0.0057
	Commercial vs Medicare	0.668 (0.533, 0.839)	
	Commercial vs Other or unknown	0.845 (0.541, 1.321)	
	Medicaid vs Medicare	0.762 (0.476, 1.219)	
	Medicaid vs Other or unknown	0.963 (0.531, 1.747)	
	Medicare vs Other or unknown	1.264 (0.777, 2.058)	
Congestive heart failure	Yes vs No	1.982 (1.093, 3.595)	0.0243
Hypothyroidism	Yes vs No	1.285 (1.034, 1.596)	0.0236
Coagulopthy	Yes vs No	2.589 (1.200, 5.586)	0.0153

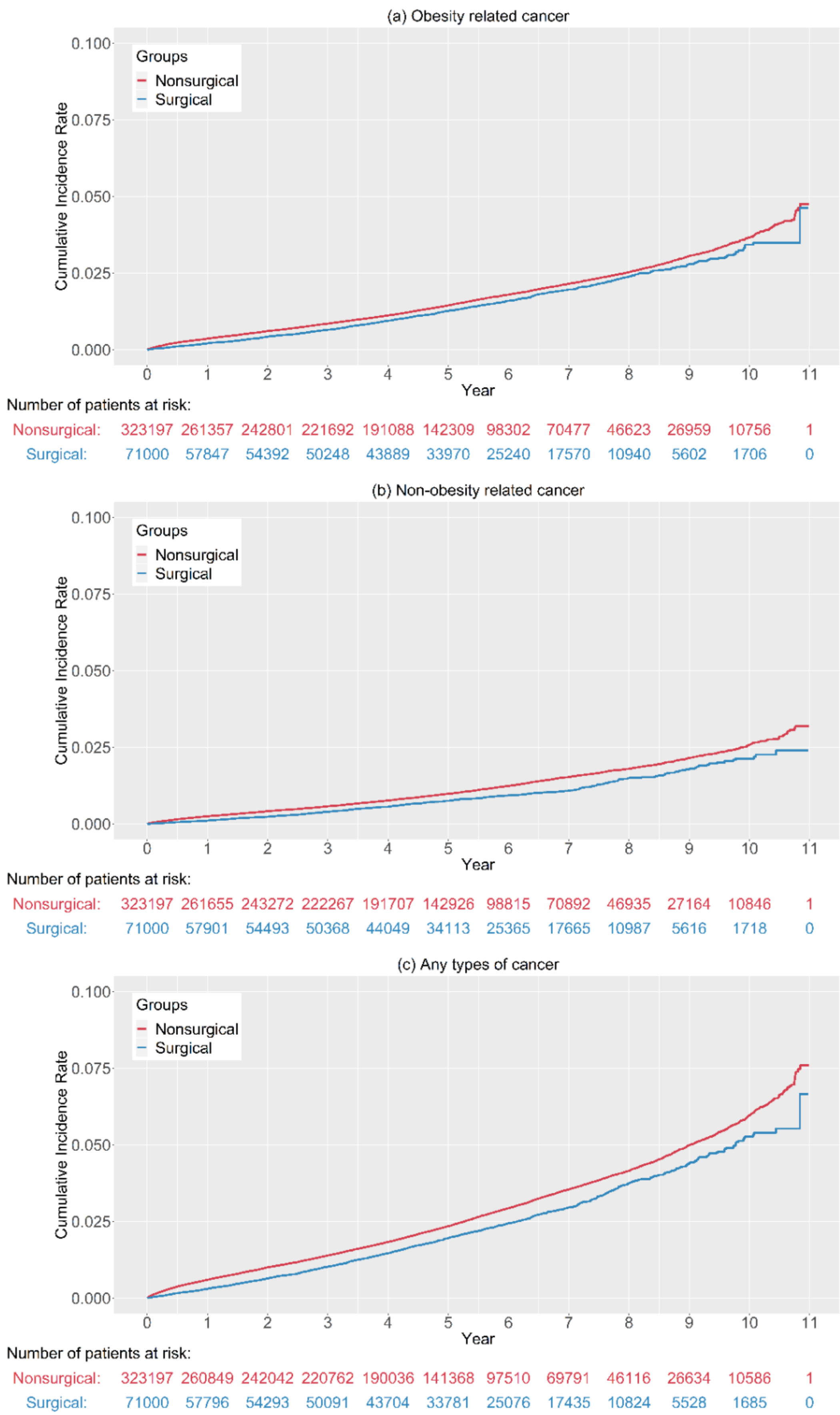
*: P-value was the type-3 p-value from multivariable Fine-Gray model.

Table 4. Estimated hazard ratios of explanatory variables and their 95% confidence intervals for post-operative non-obesity related cancer development based on a multivariable Fine-Gray model

Variable	Level	Hazard Ratio with 95% Confidence Interval	P-value*
Patients' groups	Surgical vs Non-surgical	**0.819 (0.751, 0.893)**	<.0001
Age (continuous)	Unit=1 year	1.074 (1.070, 1.077)	<.0001
Gender	Female vs Male	0.751 (0.704, 0.801)	<.0001
Race/ethnicity	Asian, non-Hispanic vs Black, non-Hispanic	0.818 (0.529, 1.265)	<.0001
	Asian, non-Hispanic vs Hispanic	0.923 (0.592, 1.438)	
	Asian, non-Hispanic vs Other	0.689 (0.445, 1.068)	
	Asian, non-Hispanic vs White, non-Hispanic	0.483 (0.314, 0.744)	
	Black, non-Hispanic vs Hispanic	1.128 (0.979, 1.299)	
	Black, non-Hispanic vs Other	0.842 (0.743, 0.954)	
	Black, non-Hispanic vs White, non-Hispanic	0.590 (0.535, 0.650)	
	Hispanic vs Other	0.747 (0.643, 0.868)	
	Hispanic vs White, non-Hispanic	0.523 (0.460, 0.595)	
	Other vs White, non-Hispanic	0.701 (0.631, 0.779)	
Insurance	Commercial vs Medicaid	0.847 (0.765, 0.937)	<.0001
	Commercial vs Medicare	0.856 (0.792, 0.926)	
	Commercial vs Other or unknown	1.042 (0.911, 1.191)	
	Medicaid vs Medicare	1.012 (0.898, 1.139)	
	Medicaid vs Other or unknown	1.230 (1.049, 1.443)	
	Medicare vs Other or unknown	1.216 (1.052, 1.407)	
Alcohol abuse	Yes vs No	1.165 (0.972, 1.397)	0.0989
Tobacco use	Yes vs No	2.143 (1.986, 2.311)	<.0001
Any other comorbidities	Yes vs No	1.063 (0.978, 1.155)	0.1516

*: P-value was type-3 p-value from multivariable Fine-Gray hazards model.


Obesity records
Excluded
Missing UPID or age<18
Missing or unknown gender (N=12)
Duplicated records (N=4,506)
Non-surgical comparison records (N=1,691,624)
Bariatric surgery records (N=97,003)
Surgery types: revision, RYGB, LSG, AGB.
Earliest records for each patient (N=884,257)
Earliest records for each patient (N=76,354)
Excluded
In-hospital death
Tobacco or alcohol use
AIDS, lymphoma, metastatic cancer or solid tumor w/out metastasis diagnosis
Any type of cancer
Excluded
In-hospital death
Tobacco or alcohol use
AIDS, lymphoma, metastatic cancer or solid tumor w/out metastasis diagnosis
Any type of cancer
Non-surgical comparison group (N=694,500)
Bariatric surgical group (N=71,000)
Matched with surgical group on 5:1 ratio without replacement, and gender, age and race\ethnicity were exactly matched
Matched non-nonsurgical comparison group (N=323,197)
Track cancer incidence in follow-up records
Track cancer incidence in follow-up records


(a) Obesity related cancer
Groups
Nonsurgical
Surgical
Cumulative Incidence Rate
0.100
0.075
0.050
0.025
0.000
0 1 2 3 4 5 6 7 8 9 10 11
Year
Number of patients at risk:
Nonsurgical: 323197 261357 242801 221692 191088 142309 98302 70477 46623 26959 10756 1
Surgical: 71000 57847 54392 50248 43889 33970 25240 17570 10940 5602 1706 0
(b) Non-obesity related cancer
Groups
Nonsurgical
Surgical
Cumulative Incidence Rate
0.100
0.075
0.050
0.025
0.000
0 1 2 3 4 5 6 7 8 9 10 11
Year
Number of patients at risk:
Nonsurgical: 323197 261655 243272 222267 191707 142926 98815 70892 46935 27164 10846 1
Surgical: 71000 57901 54493 50368 44049 34113 25365 17665 10987 5616 1718 0
(c) Any types of cancer
Groups
Nonsurgical
Surgical
Cumulative Incidence Rate
0.100
0.075
0.050
0.025
0.000
0 1 2 3 4 5 6 7 8 9 10 11
Year
Number of patients at risk:
Nonsurgical: 323197 260849 242042 220762 190036 141368 97510 69791 46116 26634 10586 1
Surgical: 71000 57796 54293 50091 43704 33781 25076 17435 10824 5528 1685 0

Highlights:

- The risk of cancer after bariatric surgery for patients with obesity were studied
- Bariatric Surgery patients had a lower risk of cancer than non-surgery patients
- Roux-en-Y gastric bypass patients had the lowest risk of any type of cancer
- Expansion of bariatric indications for reducing the risk of cancer may be warranted