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Esophageal adenocarcinoma after obesity surgery in a population-based cohort study

Maret-Ouda, John; Tao, Wenjing; Mattsson, Fredrik; Brusselaers, Nele; El-Serag, Hashem B; Lagergren, Jesper

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ABSTRACT

Background: Obesity is strongly associated with esophageal adenocarcinoma (EAC), yet whether weight loss reduces the risk of EAC is unclear.

Objectives: To test the hypothesis that the risk of EAC decreases following weight reduction achieved by obesity surgery.

Setting: Nationwide register-based cohort study

Methods: This study included a majority of individuals who underwent obesity surgery in Sweden in 1980-2012. The incidence of EAC following obesity surgery was compared to the incidence in the corresponding background population of Sweden by means of calculation of standardized incidence ratios (SIRs) with 95% confidence intervals (CIs). The risk of EAC after obesity surgery was also compared with the risk in non-operated obese individuals by means of multivariable Cox regression, providing hazard ratios (HRs) with 95% CIs, adjusted for potential confounders.

Results: Among 34,437 study participants undergoing obesity surgery and 239,775 person-years of follow-up, 8 cases of EAC occurred (SIR 1.6, 95% CI 0.7-3.2). No clear trend of decreased SIRs was seen in relation to increased follow-up time after surgery. The SIR of EACs (n=53) among 123,695 non-operated obese individuals (673,238 person-years) was increased to a similar extent as in the obesity surgery cohort (SIR=1.9, 95% CI 1.4-2.5). Cox regression showed no difference in risk of EAC between operated and non-operated participants (adjusted HR=0.9, 95% CI 0.4-1.9).

Conclusions: The risk of EAC might not decrease following obesity surgery, but even larger studies with longer follow-up are needed to establish this association.

Keywords: Obesity, Bariatric surgery, Cancer, Neoplasm, Weight loss

INTRODUCTION

The incidence of adenocarcinoma of the esophagus (EAC), including the gastroesophageal junction, has increased rapidly in the Western world during the last four decades.[1, 2] The incidence of EAC in Sweden in 2013 was 10.9 cases per 100,000 men and 2.6 cases per 100,000 women.[3] The increase in EAC parallels the globally increasing prevalence of obesity (body mass index [BMI] >30).[4] EAC appears to be strongly associated with increased BMI,[5, 6] and this association is seemingly linear.[7] Yet, it is uncertain whether weight loss counteracts EAC development. This uncertainty is explained by difficulties in assessing weight loss due to limited effects of lifestyle changes on BMI and variations in BMI over time, together with the need for large studies with long follow-up to assess this association. Obesity surgery might be a useful means of assessing the effects of weight loss, since on group level it results in substantial and persistent reduction in BMI and the weight loss is initiated at a specific date.[8] Some, but not all investigations have indicated a possibly decreased risk of cancer in general after successful obesity surgery;[9-12] but any preventive effect of obesity surgery on the specific risk of developing EAC is unknown. A recent systematic review identified only 11 cases of EAC following obesity surgery in the literature, and these cases were mainly derived from case reports, prohibiting analysis of the risk of EAC.[13] The objective of this study was to test the hypothesis that the risk of EAC decreases following obesity surgery in a nationwide Swedish cohort study.

METHODS

Study design

This was a population-based cohort study including obese individuals aged between 18 and 65 years who underwent obesity surgery in Sweden between January 1, 1980 and December 31, 2012 (*obesity surgery cohort*). Obesity surgery was introduced in routine healthcare in Sweden in 1980 and individuals with a BMI ≥35 were considered potential surgical candidates. Two external comparison cohorts were used: the corresponding background Swedish population and obese individuals who did not undergo obesity surgery (*obese non-surgery cohort*). The participants of both the obesity surgery cohort and the obese non-operated cohort were identified from the Swedish Patient Registry; the obesity surgery cohort by a diagnosis code of obesity as well as an obesity surgery code, and the obese non-surgery cohort by a diagnosis code of obesity. The background population was derived from the Swedish Registry of the Total Population. All EACs occurring during follow-up of the cohorts, as well as those of the background population, were identified from the Swedish Cancer Registry. Any cases of EAC discovered at autopsy were excluded from all three cohorts to avoid ascertainment bias. Censoring of cohort members no longer at risk of EAC in the Cancer Registry due to death or emigration was enabled by data linkage to the Swedish Causes of Death Registry and the Registry of the Total Population, respectively. The 10-digit personal identity number, uniquely assigned to all Swedish residents upon birth or immigration, was used for all register linkages and for collection of medical records from patients who developed EAC after obesity surgery.[14] The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Data collection

The Swedish Patient Registry was used to identify participants of the obesity surgery cohort and the obese non-operated cohort. This register was initiated in 1964 and contains information regarding in-hospital and outpatient specialist care in Sweden, including diagnoses and surgical procedures. The percentage of the Swedish population covered by this register was 85% in 1983 and 100% from 1987 onwards in terms of in-hospital care, while the data on outpatient specialist care have been nationwide complete since 2001.[15] Studies have shown excellent validity of the data regarding the recorded information for both diagnoses and surgical procedures.[15, 16] Obesity was defined by the diagnosis codes 277, 278A, and E66 in the International Classification of Diseases (ICD) versions 8, 9, and 10, respectively. Obesity surgery codes representing the most commonly used procedures, i.e. gastric bypass, vertical banded gastroplasty, and gastric banding (both open and laparoscopic techniques), were based on the Swedish and NOMESCO Classification of Surgical Procedures. The surgery codes were 4751 and 4753 before 1997 and JDF00, JDF01, JDF10, JDF11, JDF20 and JDF21 from 1997 onwards.

The Swedish Cancer Registry was used to identify EAC, including the gastro-esophageal junction, using the ICD-7 codes 150 and 1511, and WHO/HS/CANC/24.1 histology code 096. This register contains data on all malignant tumors diagnosed in Sweden since 1958 and includes date of diagnosis, site of tumor (translated to ICD-7), and histological type of tumor. All physicians and pathologists are obliged to report all cancer cases, and the register has been verified to have 98% nationwide completeness in terms of EAC.[17]

The Swedish Causes of Death Registry contains data regarding all deceased Swedish residents since 1952 and has a 99.2% completeness of cause-specific death.[18] Data from this register were used to censor individuals in the cohorts from follow-up at the date of death.

The Registry of the Total Population was used to identify the background population and to censor cohort members who emigrated during follow-up. This register has 100% nationwide completeness and is continuously updated.[19]

Medical records were retrieved from the hospital departments for individuals in the obesity surgery cohort who developed EAC. These records were used to assess presenting symptoms, BMI, treatment and outcomes.

Statistical analysis

Standardized incidence ratio: Follow-up in the obesity surgery cohort was measured from the date of admission for obesity surgery, until the date of EAC, death, emigration, or end of the study period, whichever occurred first. Follow-up time for the obese non-surgery cohort was measured from the first date of obesity diagnosis until the date of obesity surgery, EAC, death, emigration, or end of the study period, whichever came first. The number of EACs in the obesity surgery cohort and in the obese non-surgery cohort was compared to their corresponding background population by means of calculation of standardized incidence ratios (SIRs) and 95% confidence intervals (CIs). SIRs were calculated by dividing the observed number of EACs in the obesity surgery cohort and the obese non-surgery cohort by the expected number of EACs using direct standardization. The expected number of EACs was calculated separately for the obesity surgery cohort and the obese non-surgery cohort, using the incidence of EAC in the background population of the corresponding age (categorized in 10-year intervals), sex (male or female), and calendar year (categorized by each year) distributions as the members of these cohorts, multiplied by the person-time in each cohort. We also performed predefined analyses stratified for sex (male and female), age

at inclusion (18-41 years and 42-65 years, a cut-off chosen as half of the possible age range at inclusion [18-65 years]), and follow-up time after surgery or obesity diagnosis (≤5 years, >5-10 years, and >10 years).

Cox regression: The risk of EAC in the obesity surgery cohort was also directly compared with the risk of EAC in the obese non-surgery cohort by means of multivariable Cox regression analysis, providing hazard ratios (HRs) and 95% CIs. The HRs were adjusted for age (continuous variable), sex (male or female), calendar period (continuous variable), years of formal education (≤9 years, 10-12 years, or >12 years), history of chronic obstructive pulmonary disorder (yes or no, proxy for tobacco smoking), and history of diabetes mellitus (yes or no). Since gastric bypass is known to improve GERD, while this effect is less clear following restrictive procedures (vertical banded gastroplasty and gastric banding),[20] we also conducted analyses for these procedures separately. To evaluate the proportional hazard assumption, the correlation between Schoenfeld residuals and the ranking of individual failure times was calculated for each covariate in the unadjusted and adjusted models. None of the covariates had a statistically significant association with these residuals or failure time (p-value >0.05), which supports the proportional hazards assumption. All statistical analyses were conducted using the statistical software SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Participants

The obesity surgery cohort included 34,437 unique individuals and 239,775 person-years at risk. Gastric bypass was the dominant procedure (n=25,536, 74%), followed by vertical banded gastroplasty (n=4,889, 14%) and gastric banding (n=4,012, 12%). The obese non-surgery cohort included 123,695 unique individuals and 673,238 person-years at risk. The distribution of age, follow-up time, year of inclusion, education level, chronic obstructive pulmonary disorder and diabetes were similar in these two cohorts, while there were fewer men in the obesity surgery cohort (24% versus 33%) (Table 1). The maximum follow-up time in both cohorts was 33 years.

In the obesity surgery cohort, 8 cases of EAC occurred, including 4 cases following gastric banding (3 open and 1 laparoscopic), 2 cases following open vertical banded gastroplasty and 2 cases following open gastric bypass (Tables 1 and 2). Seven patients (88%) were male, and the median age at EAC diagnosis was 63.5 years. The EACs were diagnosed within median 9.2 years after obesity surgery. The mean BMI at EAC diagnosis was 34.4 (range 25-44) and 5 of the 7 patients were still obese (BMI >30) where BMI was available. The mean BMI loss following obesity surgery was 6.3 for the 6 patients where pre-surgery BMI was available. The EAC patients presented with dyspepsia, nausea, melena or dysphagia (2 patients each), anemia, weight loss, hematochezia, or vomiting (1 patient each).

In the obese non-surgery cohort, 53 cases of EAC occurred, including 40 males (75%), with a median age of 60.0 years and median 5.9 years latency between obesity and EAC diagnosis (Table 1).

The rate of EAC following gastric banding or vertical banded gastroplasty (grouped) was 3.9 cases per 100,000 persons and year, and the rate of EAC following gastric bypass was 2.0

cases per 100,000 persons and year. The overall rate of EAC in the background population during the follow-up period was 5.4 per 100,000 persons and year.

Risk of esophageal adenocarcinoma

Obesity surgery cohort

The overall SIR of EAC was 1.6 (95% CI 0.7-3.2) in the obesity surgery cohort (Table 3). The SIR did not change significantly when stratifying for follow-up time after surgery. The point estimates of EAC were higher for men than women and for older individuals than younger, but the confidence intervals overlapped (Table 3).

Obese non-surgery cohort

The overall SIR was 1.9 (95% CI 1.4-2.5) in the obese non-surgery cohort (Table 3). The SIRs were stable over time after obesity diagnosis. The point estimates were higher among older than younger participants, but without statistical significance, and no sex differences were seen (Table 3).

Obesity surgery cohort compared to the obese non-surgery cohort

The crude HR indicated a decreased HR of EAC comparing obese individuals who underwent obesity surgery with obese individuals not undergoing such surgery (unadjusted HR 0.4, 95% CI 0.2-0.9), but the HR approached 1 after multivariable adjustment (adjusted HR 0.9, 95% CI 0.4-1.9) (Table 4). Adjusted HRs following vertical banded gastroplasty or gastric banding (6 cases) was 1.0 (95% CI 0.4-2.6), and 0.5 (95% CI 0.1-2.3) after gastric bypass (2 cases).

DISCUSSION

This study did not provide evidence for the hypothesis of a decreased risk of EAC after obesity surgery. The point estimates of EAC were increased after obesity surgery compared to the background population, and similar to non-operated obese individuals.

The nationwide coverage with complete follow-up of a large obesity surgery cohort that was compared with the corresponding background population and non-operated obese are among the methodological strengths of the study. However, despite a substantial number of cohort members, the main limitation is the low statistical precision, which was due to the low number of new EACs and a limited long-term follow-up of the operated patients.

This is nevertheless the largest study to date which provides the highest number of EAC cases described in the literature, and it is to the best of our knowledge, the first controlled study on the topic. There is a risk of selection bias in the obese non-surgery cohort, since only a limited portion of all obese patients received a diagnosis code for obesity in the Patient Registry, while for the obesity surgery cohort the obesity diagnosis was the reason for the surgery. Thus, the obesity surgery cohort might not be entirely comparable to the obese non-surgery cohort regarding potential confounding factors. However, the adjustment for confounders changed the point estimates from 0.4 to 0.9, reducing some of this concern. Other limitations were the lack of data on BMI.[21] However, another study of obesity surgery in Sweden which included a portion of the participants of the present study, found an average decrease in BMI 10 years following surgery (n=2010) from 41.9 to 35.3 (15.7%), compared to an increase from 39.9 to 40.8 (2.3%) in the non-surgery group (n=2037).[22] This illustrates the great difference in weight change in the obesity cohort and the obese non-surgery cohort of the present study, although it also suggests that patients may still remain obese, albeit to a lesser degree, following obesity surgery. However, the lack of individual BMI data meant that we

could not separate out patients with "successful" obesity surgery (i.e., BMI <30). Finally, we did not have information on Barrett´s esophagus or gastroesophageal reflux disease, but these conditions might be seen as variables in the pathway between the association between BMI and weight loss and EAC, thus the lack of this information might not be a major concern.

Obesity surgery might be seen as a human model for research addressing the consequences of weight loss, since this surgery is clearly more effective than non-surgical interventions for weight loss, and the weight loss starts from a certain date.[8, 23] Yet, the available literature assessing the risk of EAC after obesity surgery is limited. Only 11 patients with EAC occurring after obesity surgery are known in the literature.[13] The mean age at EAC diagnosis in these patients was lower (54 years), and the mean latency period between obesity surgery and EAC diagnosis was shorter (5.5 years) than in the present study (63 years and 9.2 years, respectively).[13] The only previous cohort study included 2,875 individuals following obesity surgery and 3 cases of high-grade dysplasia or EAC (0.1%), but that study did not include any control group, hence relative risk estimates were not possible to calculate.[24]

There are other mechanisms besides weight loss that might influence the association between obesity surgery and EAC. Severe obesity typically develops over many years, and might result in a persistently increased abdominal pressure, leading to long-term and severe gastroesophageal reflux disease, which might be irreversible at the time of obesity surgery. It is also possible that the anatomic changes following obesity surgery might influence the future risk of EAC, although the extent and direction of any such influence is uncertain. Gastric bypass can reduce symptoms of gastroesophageal reflux disease as well as acid exposure in patients with Barrett's esophagus,[25, 26] and there are reports of regression of Barrett's esophagus following gastric bypass.[27] However, there are also studies of bile reflux

in the gastric pouch following gastric bypass,[28, 29] which is a risk factor for EAC.[30-32] For gastric banding and vertical-banded gastroplasty, some studies have shown an increased risk of gastroesophageal reflux disease and Barrett's esophagus,[33] risk of food and gastric acid stasis causing chronic mucosal irritation,[34, 35] and local irritation due to the presence of the gastric band.[36] A study following patients up to 18 months after gastric banding found an increased risk of esophageal dysmotility.[37] Moreover, although most individuals lose weight after obesity surgery, they rarely become non-obese (BMI <30). In the recent systematic review and in the present study, BMI at the time of EAC diagnosis was typically ≥30,[24, 38, 39] which could partly explain the possible lack of a decreased risk of EAC compared to the background population. We attempted to assess the risk of EAC following the different types of obesity surgery procedures, and these results indicated no obvious differences between the procedures, although the statistical power was low.

In a clinical setting, this study indicates that patients following obesity surgery comprise a patient group that remains at increased risk of EAC. This in turn indicates a need for awareness, especially since the symptoms might be non-characteristic or attributed to the obesity surgery itself, which could lead to delayed diagnosis and treatment.[40]

CONCLUSIONS

This population-based nationwide Swedish cohort study of nearly 0.25 million person-years at risk did not find evidence of any decreased risk of EAC following obesity surgery when compared to the background population or non-operated obese individuals. However, the results must be interpreted cautiously due to the limited statistical power, and larger cohort studies with longer follow-up are warranted.

DISCLOSURES

JMO, WT, FM, NB, HBES, JL: Nothing to disclose.

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Table 1. Characteristics of an obesity surgery cohort and an obese non-surgery cohort, identified in the Swedish Patient Registry in 1980-2012, and the distribution of esophageal adenocarcinoma (EAC) in these cohorts.

	Obesity surgery Number=34,437	**Obese non-surgery Number=123,695**
Person-years of follow-up	239,775	673,238
Age at inclusion, median years (IQR*)	40 (33-48)	43 (32-54)
Male sex, number (%)	8,243 (24)	40,782 (33)
Year of inclusion, median (IQR*)	2009 (2002-2011)	2007 (2002-2010)
Follow-up time in years, median (IQR*)	3.7 (1.8-9.7)	3.5 (1.3-7.3)
Educational level <9 years, number (%)	6,786 (20)	30,440 (25)
10-12 years, number (%)	20,650 (60)	64,519 (53)
>12 years, number (%)	6,873 (20)	26,932 (22)
Chronic obstructive pulmonary disorder, number (%)	436 (1)	2,963 (2)
Diabetes, number (%)	4,536 (13)	18,997 (15)
Cases of EAC (number)	8	53
Age at cancer diagnosis, median years (IQR*)	63.5 (61.5-67.5)	60.0 (56.0-66.0)
Time after inclusion, median years (IQR*)	9.2 (6.6-15.0)	5.9 (2.3-10.1)
Male, number (%)	7 (88)	40 (75)

* Interquartile range

Table 2. Clinical characteristics of individuals developing esophageal adenocarcinoma (EAC) following obesity surgery.

Patient	Sex	Year of obesity surgery	Age at obesity surgery	Obesity surgery technique	Pre-surgery BMI*	ΔBMI*	BMI* at EAC	Year of EAC diagnosis	Age at EAC diagnosis	Years between obesity surgery and EAC	Symptoms	Tumor stage	Years of follow-up after EAC	Treatment	Outcome
1	Female	1998	40	Open vertical banded gastroplasty	42	5	37	2007	51	10	Dyspepsia, nausea	TXN3M1	0.1	None	Died of EAC
2	Male	1998	52	Open vertical banded gastroplasty	34	3	31	2009	63	11	Melena, anemia	TXNXM1	1.2	CTx[#] + RTx[┼]	Died of EAC
3	Male	1985	49	Open gastric banding	46	7	39	2006	71	22	Dysphagia, weight loss	T1N0M0	8.7	CTx[#] + surgery	Cured
4	Male	1986	55	Open gastric banding	Missing	Missing	Missing	1994	64	9	Asymptomatic	T1N0M0	0.6	Surgery	Died of EAC
5	Male	1988	54	Open gastric banding	Missing	Missing	44	2007	74	19	Nausea, vomiting	TXN3M1	0.1	None	Died of EAC
6	Male	2000	56	Laparoscopic gastric banding	38	0	38	2009	64	8	Melena, hematochezia	T3N0M0	5.2	CTx[#] + RTx[┼] + surgery	Cured
7	Male	2006	59	Open gastric bypass	35	10	25	2011	65	5	Dyspepsia	T4bN0M0	1.8	CTx[#] + surgery	Died of EAC
8	Male	2008	56	Open gastric bypass	40	13	27	2012	60	4	Dysphagia	T3N2M0	2.5	CTx[#] + surgery	Died of EAC

* Body mass index, EAC esophageal adenocarcinoma, [#] chemotherapy, [┼] radiotherapy

Table 3. Standardized incidence ratios (SIR) and 95% confidence intervals (CIs) of esophageal adenocarcinoma (EAC) after obesity surgery and in non-operated obese participants compared with their corresponding background population.

	Obesity surgery cohort		**Obese non-surgery cohort**	
Model	EAC (number)	SIR (95% CI)	EAC (number)	SIR (95% CI)
All	8	1.6 (0.7-3.2)	53	1.9 (1.4-2.5)
Sex				
Male	7	2.4 (0.9-4.9)	40	1.9 (1.3-2.6)
Female	1	0.5 (0.0-2.8)	13	1.9 (1.0-3.3)
Age at inclusion				
18-41 years	1	0.9 (0.0-5.3)	7	3.5 (1.4-7.2)
42-65 years	7	1.8 (0.7-3.7)	46	1.8 (1.3-2.3)
Follow-up				
≤ 5 years	2	1.3 (0.2-4.8)	23	1.8 (1.2-2.7)
> 5-10 years	3	3.1 (0.6-9.1)	16	2.1 (1.2-3.4)
> 10 years	3	1.2 (0.2-3.5)	14	1.8 (1.0-3.0)

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