Title: Decreased risk of esophageal adenocarcinoma after gastric bypass surgery in a cohort study from three Nordic countries

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Running head: Gastric bypass and esophageal adenocarcinoma

Abstract

Objective: To test the hypothesis that bariatric surgery decreases the risk of esophageal and cardia adenocarcinoma.

Background: Obesity is strongly associated with esophageal adenocarcinoma and moderately with cardia adenocarcinoma, but whether weight loss prevents these tumors is unknown.

Methods: This population-based cohort study included patients with an obesity diagnosis in Sweden, Finland, or Denmark. Participants were divided into a bariatric surgery group and a non-operated group. The incidence of ECA was first compared with the corresponding background population by calculating standard incidence ratios (SIR) with 95% confidence intervals (CI). Second, the bariatric surgery group and the non-operated group were compared using multivariable Cox regression, providing hazard ratios (HR) with 95% CI, adjusted for sex, age, comorbidity, calendar year, and country.

Results: Among 748,932 participants with an obesity diagnosis, 91,731 underwent bariatric surgery, predominantly gastric bypass (n=70,176; 76.5%). The SIRs of ECA decreased over time following gastric bypass, from SIR=2.2 (95% CI 0.9-4.3) after 2-5 years to SIR=0.6 (95% CI <0.1-3.6) after 10-40 years. Gastric bypass patients were also at a decreased risk of ECA compared to non-operated patients with obesity (adjusted HR=0.6, 95% CI 0.4-1.0 [0.98]), with decreasing point estimates over time. Gastric bypass was followed by a strongly decreased adjusted risk of esophageal adenocarcinoma (HR=0.3, 95% CI 0.1-0.8), but not of cardia adenocarcinoma (HR=0.9, 95% CI 0.5-1.6), when analyzed separately. There were no consistent associations between other bariatric procedures (mainly gastroplasty, gastric banding, sleeve gastrectomy, and biliopancreatic diversion) and ECA.

Conclusion: Gastric bypass surgery may counteract the development of esophageal adenocarcinoma in morbidly obese individuals.

Keywords: Bariatric surgery; weight loss; esophageal neoplasm; cardia neoplasm.

Introduction

Obesity is a growing global public health problem, affecting >600 million of the world's adult population (1). Obesity increases the risk of several malignancies, but the association with esophageal adenocarcinoma is particularly strong, and the association with cardia adenocarcinoma is moderate (2). Esophageal and cardia adenocarcinoma (ECA) carry a poor prognosis (<20% 5-year survival) and the incidence has increased rapidly during the last four decades (3). Except for systemic carcinogenic properties of obesity through inflammatory and metabolic alterations, there is also a mechanism specific to ECA where excess intra-abdominal adiposity increases the intra-gastric pressure, which promotes gastro-esophageal reflux, the other main risk factor for ECA (4).

It is unknown if weight loss reduces the risk of ECA. Long-term effects of non-surgical weight loss are difficult to assess due to time-varying, limited, and short-lasting weight reduction. In contrast, bariatric surgery results in substantial, continuous, and sustainable weight loss starting from a specific date (5). Gastroplasty, gastric banding, and gastric bypass have been the main bariatric procedures for several decades, but gastric bypass has shown more favorable results (6) and has become the dominating procedure. Only more recently, sleeve gastrectomy has become an increasingly common alternative (7,8). Research has indicated that bariatric surgery decreases the risk of certain obesity-related tumors, e.g., breast and endometrial cancer (9–12), but it is unclear if it prevents ECA. This knowledge gap is mainly due to low statistical power and short follow-up in the available literature (13).

We aimed to conduct the first study with sufficient power and length of follow-up to test the hypothesis that bariatric surgery decreases the risk of ECA, and more so for esophageal adenocarcinoma than for cardia adenocarcinoma. We hypothesized a gradually decreased risk over time after surgery, and this to a larger extent after gastric bypass than other bariatric procedures because of greater weight loss and antireflux properties.

Methods

Design

This population-based cohort study included all patients with an obesity diagnosis (Supplementary Table 1) recorded in any of the national patient registries in Sweden, Finland, or Denmark. The diagnosis of obesity was determined by a physician, who also recorded the diagnosis in the patient registry. The total study period spanned from 1980 until the end of 2019, but the start year varied between the three countries depending on when specific procedural codes for bariatric surgery became available (1980 in Sweden, 1985 in Finland, and 1996 in Denmark). The exposure was bariatric surgery and the main outcome was ECA. The cohort of patients with an obesity diagnosis was divided into two groups, one made up of patients who underwent bariatric surgery and one with those who did not undergo such surgery. Individuals were excluded if bariatric surgery was performed before the age of 18 years or if there was a record of ECA prior to the obesity diagnosis. Data came from an updated version of the Nordic Obesity Surgery Cohort (NordOSCo), which we have described in detail elsewhere (14) and used for other studies examining outcomes of bariatric surgery (15). NordOSCo contains merged information from the patient registries, cancer registries, population registries, and the cause of death registries in all participating countries. These registries do not record body mass index (BMI). The study was approved by all relevant ethical committees, data inspectorates, and governmental agencies in the three countries (14).

Exposures

Indications for bariatric surgery in the Nordic countries are BMI >40 or BMI >35 combined with at least one serious obesity-associated co-morbidity. Bariatric surgery included the procedures of gastric bypass (Roux-en-Y gastric bypass), gastroplasty (Vertical banded gastroplasty), gastric banding, sleeve gastrectomy, and biliopancreatic diversion (Supplementary Table 2). Gastric bypass and other bariatric procedures except for gastric bypass were also analyzed separately. Data on bariatric surgery were retrieved from the national patient registries, which since 1997 have used the Nordic Medico-Statistical Committee Classification of Surgical Procedures (NOMESCO) for coding surgical procedures. Country-specific procedural codes were used prior to the year 1997 in Finland and Sweden (Supplementary Table 3). A recent validation study of 938 patients having undergone bariatric surgery in Sweden showed 97% concordance between the data in the Swedish Patient Registry and operation charts (16).

Outcomes

The main outcome was the incidence of ECA after bariatric surgery, particularly regarding changes in risk over time. Esophageal adenocarcinoma and gastric cardia adenocarcinoma were combined to preserve statistical power, and was motivated by difficulties separating them in clinical practice (17), similar incidence trends, and shared risk factors, i.e. obesity, particularly abdominal adiposity (18), and gastroesophageal reflux disease (4). Secondary outcomes were the separate incidence rates of esophageal adenocarcinoma and cardia adenocarcinoma. The incidence rates of the studied tumors were identified from the national cancer registries (Supplementary Table 4). The cancer registries are over 96% complete overall (14), and for ECA, the Swedish Cancer Registry has over 98% completeness and 100% for morphological confirmation (17). Cardia carcinoma includes Siewert type 1, 2, and 3 tumors in the Nordic cancer registries. Censoring of follow-up due to mortality was enabled by linkage to the cause of death registries, which have 100% completeness for the date of death (14).

Covariates

Five covariates were considered potential confounders and categorized as follows: Sex (male or female), age (continuous), comorbidity (Charlson Comorbidity Index score 0 or ≥1), calendar year of entry into the cohort (continuous), and country (Sweden, Finland, or Denmark). Data on these covariates were retrieved from the national patient registries. For comorbidity, we used the most well-validated version of the Charlson Comorbidity Index (19,20). The patient registries in the Nordic countries record all diagnoses in inpatient hospital care and outpatient specialized care with positive predictive values ranging between 85-95% in Sweden (21), 75-99% in Finland (22), and 73-88% in Denmark (23).

Statistical analysis

The first year after cohort entry was excluded to avoid detection bias. Thus, follow-up started one year after the obesity diagnosis and ended at the date of ECA diagnosis, mortality, or end of the study period (December 31, 2019), whichever came first. In the non-operated group with obesity, the date of any bariatric surgery was an additional end date of follow-up. Patients initially in the non-operated group could thus cross over and contribute person-time to the operated group from the date of bariatric surgery. Patients with a first obesity diagnosis before 18 years of age were included in the study cohort the year they turned 18 or when a year had passed after the obesity diagnosis (if less than a year remained until the patient turned 18 at the time of diagnosis).

Two statistical approaches were used to estimate the relative risks of the outcomes. First, the incidence of ECA among the group of patients who had undergone bariatric surgery and the incidence of ECA among the group of non-operated patients with morbid obesity were compared with the incidence of ECA in the corresponding Swedish background population.

Standardized incidence ratios (SIR) with 95% confidence intervals (CI) were calculated by dividing the observed number of cases within the operated and non-operated obesity patient groups by the expected number of cases for each group separately. The expected numbers were derived from the background population of the corresponding sex (male or female), age (5-year categories), and calendar period (1980-1984, 1985-1989, 1990-1994, 1995-1999, 2000-2004, 2005-2009, 2010-2014 and 2015-2019). The analyses were stratified by four pre-defined follow-up periods: 1-2 years, >2-5 years, >5-10 years, and >10-40 years.

In the second statistical approach, the incidence of ECA among patients who had undergone bariatric surgery was compared with the incidence of ECA among non-operated patients with obesity. Cox regression analysis provided hazard ratios (HR) with 95% CI. Except for a crude model (without adjustments), a multivariable model adjusted for the five covariates presented and categorized above. The proportional hazard assumption was checked by computing the Schoenfeld residuals. The assumption was met both for the model examining all bariatric surgery procedures and for the models examining gastric bypass and other bariatric surgery procedures separately. To evaluate if associations were modified by covariates, an interaction term with the main exposure and the potential effect modifier was included in the multivariable model, and HRs were derived within each stratum of the modifier. Interaction terms were introduced for separate models of follow-up categories (1-2 years, >2-5 years, >5-10 years, and >10-40 years), sex (male and female), age (two groups divided by median value), comorbidity (Charlson Comorbidity Index score 0 or ≥1), calendar year (two groups divided by median value), and country (Sweden, Finland, and Denmark).

The data management and statistical analyses were performed by a senior biostatistician (GS) using the statistical package STATA (version MP 15.01, StataCorp, College Station, TX).

The statistical analyses followed a detailed study protocol, created and agreed upon by all authors before initiating any analysis.

Results

Patients

The cohort consisted of 748,932 individuals with an obesity diagnosis. Of these, 91,731 (12.2%) had undergone bariatric surgery, predominantly gastric bypass (n=70,176; 76.5%) and less often another bariatric surgery procedure (n=21,555; 23.5%). Characteristics of the study participants are presented in Table 1. In the total bariatric surgery group, 75.4% were women, the mean age was 42.4 years, 56.6% had no comorbidity, 3.3% had alcohol related diseases, 3.1% had tobacco related diseases, and the mean follow-up was 8.1 years. In the non-operated group, 68.6% were women, the mean age was 45.9 years, 51.2% had no comorbidity, 4.4% had alcohol-related diseases, 6.5% had tobacco smoking-related diseases, and the mean follow-up was 7.4 years. Most of the bariatric surgery was performed in Sweden (71.0%). During follow-up, 39 cases of ECA were found in the bariatric surgery group and 570 ECA cases in the non-operated group (Table 1).

Risk of esophageal or cardia adenocarcinoma compared to the background population

The bariatric surgery group had an overall increased risk of ECA compared to the corresponding background population (SIR 2.0, 95% CI 1.4-2.7), with the highest point estimate found 2-5 years after surgery (Table 2). In a separate analysis, gastric bypass had a slightly elevated risk overall of ECA compared to the background population (SIR 1.5, 95% CI 0.9-2.4), but the risk estimates decreased for each follow-up period after the 2-5-year follow-up and the SIR was 0.6 (95% CI <0.1-3.6) after >10-40 years of follow-up (Table 2). Patients who underwent another bariatric surgery procedure than gastric bypass had an increased overall risk of ECA (SIR 2.6, 95% CI 1.7-4.0), but the risk estimates decreased over time from 2-5 years after surgery (Table 2).

The non-operated group of patients with obesity had an overall increased risk of ECA compared to the corresponding background population (SIR 1.7, 95% CI 1.6-1.9). The SIRs were increased throughout the follow-up periods (Table 2).

Risk of esophageal or cardia adenocarcinoma comparing operated with non-operated patients with obesity

The overall HR of ECA was not statistically significantly decreased comparing patients who had undergone bariatric surgery with non-operated patients with morbid obesity (adjusted HR 0.9, 95% CI 0.7-1.3) (Table 3). However, those who had undergone gastric bypass had an overall reduced risk (adjusted HR 0.6, 95% CI 0.4-1.0 [0.98]), and the point estimates slightly decreased over time after gastric bypass surgery (Table 4). Patients having undergone another bariatric surgery procedure than gastric bypass were at an increased overall risk of ECA (adjusted HR 1.6, 95% CI 1.0 [1.02]-2.6), and the HRs tended to slightly increase over time (Table 4).

Separate analyses of esophageal and cardia adenocarcinoma revealed that patients who had undergone gastric bypass had a strongly decreased risk of esophageal adenocarcinoma (adjusted HR 0.3, 95% CI 0.1-0.8), but not of cardia adenocarcinoma (adjusted HR 0.9, 95% CI 0.5-1.6) (Table 3).

The HRs were consistent in all stratified analyses (Supplementary Table 5).

Discussion

This study indicates that gastric bypass surgery is followed by a decreased risk of ECA over time after surgery both compared to the corresponding background population and non-operated patients with morbid obesity. The risk reduction was limited to esophageal adenocarcinoma, and not cardia adenocarcinoma when analyzed separately.

Methodological strengths include the multinational and population-based design, the up to 40 years long and complete follow-up, and the large cohort of patients with a confirmed obesity diagnosis. The study had more post-bariatric surgery ECA cases than any previous study on the topic (13). Data on all variables, i.e. bariatric surgery, ECA, and covariates, were obtained from well-validated and nationwide complete registries (16,17). Thus, the results should be scientifically valid and generalizable to countries with similar healthcare as in the Nordic countries. Among weaknesses are that the control group with a recorded obesity diagnosis represents only a fraction of all individuals with obesity in the participating countries. However, patients obtaining an obesity diagnosis likely have more morbid obesity than obese individuals in general and thus should be more comparable with those who undergo bariatric surgery (mean BMI >40) (5). Another limitation is the lack of BMI data. The national health data registries do not record BMI data, because this would require measurement of height and weight of every patient seen in a hospital or an out-patient clinic. However, a Swedish study, including patients in the present cohort, found an average decrease in BMI from 41.9 to 35.3 (15.7%) 10 years after bariatric surgery, with stronger decreases after gastric bypass (23.8%) than after gastroplasty (16.0%) and gastric banding (12.8%), whereas the control group had a stable BMI (2.3% increase) (24). The weight changes should be similar in the present cohort. The observational study design means that confounding cannot be ruled out. However, the risk estimates were adjusted for several potential confounders, including comorbidity. The adjustment for country would account for any potential variations in screening for EAC between countries. Bias could emerge if ECA is identified earlier after bariatric surgery, but ECA is a fast-growing tumor that cause alarm symptoms, meaning that any detection bias in tumor detection should be limited. Finally, despite the large cohort size and long follow-up, the number of ECA cases was limited which reduced the precision of the estimates.

The limited number of studies that have attempted to estimate how bariatric surgery influences the risk of ECA have all had insufficient statistical power or follow-up. A recent systematic review found only 31 cases of ECA in the literature, and most of these came from case reports, prohibiting meta-analysis (13). An original study (from our group) included 8 post-bariatric surgery ECAs, and the under-powered analyses showed (as expected) no statistically significant associations (25). Two recent studies found no association between bariatric surgery and esophageal cancer, but they could not separate adenocarcinoma from squamous cell carcinoma (which is inversely associated with obesity (26)), and the follow-up was too short for assessing cancer risk (27,28).

Because of the known association between obesity and ECA, the overall increased risk among both operated and non-operated patients compared to the background population found in this study was expected and supports the validity of the data. Separate analysis of the gastric bypass group and other bariatric surgery groups showed ECA SIRs that decreased over time after surgery. When comparing patients having undergone gastric bypass with non-operated patients with obesity, the HRs were found to be consistent with the SIRs with decreased risk estimates over time after surgery. Among patients operated on with another bariatric procedure (mainly gastroplasty and gastric banding), the HRs of ECA instead increased over time after surgery, which argues against a risk reduction following these procedures. Because obesity is more strongly associated with esophageal adenocarcinoma than cardia adenocarcinoma (29–33), and gastric bypass is associated with a more substantial and long-lasting decrease in BMI and lower risk of weight regain than gastroplasty and gastric banding (24), it is not surprising that gastric bypass is associated with a more evident decrease in risk of esophageal adenocarcinoma. In addition, gastric bypass may reduce gastroesophageal reflux (13), which similarly is a stronger risk factor for esophageal adenocarcinoma than for cardia adenocarcinoma (4,34), whereas gastroplasty and gastric banding have no such antireflux effects (35,36). The long-term increased risk estimates in the "other bariatric surgery" group compared to the non-operated group may be explained by weight regain following failed surgery in a selected group with very high BMI.

Sleeve gastrectomy is becoming an increasingly common bariatric procedure (8), with comparable weight loss to gastric bypass (37,38). However, sleeve gastrectomy does not have the anti-reflux properties of gastric bypass, instead, it has been shown to promote gastroesophageal reflux (13,39). This study included only a few cases of sleeve gastrectomy due to its more recent gain in popularity, and sub-group analysis of this procedure was not possible because of too low statistical power. Whether sleeve gastrectomy is associated with ECA, and in which direction, is thus an important topic for future research.

In conclusion, this population-based cohort study, of almost 750,000 individuals with obesity diagnosis from three Nordic countries and a long and complete follow-up for up to 40 years, indicates that gastric bypass is followed by a reduced risk of esophageal adenocarcinoma.

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Tables 1-4

Table 1. Characteristics of 748,932 study patients with obesity diagnosis, including 91,731 having undergone bariatric surgery.

Characteristics	No bariatric surgery Number (%)	Bariatric surgery		
		Any bariatric surgery* Number (%)	Gastric bypass Number (%)	Other bariatric procedures ** Number (%)
Total	693,799 (100.0%)	91,731 (100.0%)	70,176 (76.5%)	21,555 (23.5%)
Sex				
Men	217,896 (31.4%)	22,615 (24.7%)	17,426 (24.8%)	5,189 (24.1%)
Women	475,903 (68.6%)	69,116 (75.4%)	52,750 (75.2%)	16,366 (75.9%)
Age at entry, mean (standard deviation)	45.9 (18.1)	42.4 (11.0)	42.5 (10.9)	42.1 (11.3)
Charlson Comorbidity score				
0	355,439 (51.2%)	51,957 (56.6%)	39,232 (55.9%)	12,725 (59.0%)
≥1	338,360 (48.8%)	39,774 (43.4%)	30,944 (44.1%)	8,830 (41.0%)
Alcohol-related diseases	30,479 (4.4%)	3,060 (3.3%)	2,301 (3.3%)	759 (3.5%)
Smoking-related diseases	44,778 (6.5%)	2,812 (3.1%)	2,254 (3.2%)	558 (2.6%)
Calendar year, mean (standard deviation)	2011 (6.5)	2011 (6.9)	2012 (3.8)	2007 (11.2)
Follow up time (years), mean (standard deviation)	7.4 (5.7)	8.1 (6.5)	6.9 (3.7)	11.9 (10.6)
Country				
Sweden	270,347 (39.0%)	65,158 (71.0%)	48,454 (69.1%)	16,704 (77.5%)
Finland	128,519 (18.5%)	8,509 (9.3%)	6,235 (8.9%)	2,274 (10.6%)
Denmark	294,933 (42.5%)	18,064 (19.7%)	15,487 (22.1%)	2,577 (12.0%)
Cancer events				
Esophageal or cardia adenocarcinoma	570 (0.1%)	39 (<0.1%)	17 (<0.1%)	22 (0.1%)
Esophageal adenocarcinoma	274 (<0.1%)	16 (<0.1%)	4 (<0.1%)	12 (0.1%)
Cardia adenocarcinoma	296 (<0.1%)	23 (<0.1%)	13 (<0.1%)	10 (0.1%)

* Gastric bypass, gastroplasty, gastric banding, sleeve gastrectomy, biliopancreatic diversion, and others.

** All bariatric procedures above except for gastric bypass.

Table 2. Standardized incidence rates (SIR) with 95% confidence intervals (CI) of esophageal or cardia adenocarcinoma among patients with obesity having undergone bariatric surgery and non-operated patients.

No bariatric surgery				
Follow-up (years)	Cohort (n)	Person-years	Cases (n)	SIR (95% CI)
>1-40	693,799	5,151,084	570	1.7 (1.6-1.9)
>1-2	639,799	663,104	56	1.8 (1.3-2.3)
>2-5	632,347	1,636,834	178	2.0 (1.8-2.4)
>5-10	463,929	1,706,782	195	1.8 (1.5-2.1)
>10-40	229,682	1,144,364	141	1.3 (1.1-1.6)
Any bariatric surgery*				
Follow-up (years)	Cohort (n)	Person-years	Cases (n)	SIR (95% CI)
>1-40	91,731	738,502	39	2.0 (1.4-2.7)
>1-2	91,731	88,844	<4**	0.7 (<0.1-3.9)
>2-5	85,853	231,166	12	2.7 (1.4-4.8)
>5-10	67,991	244,954	11	1.8 (0.9-3.2)
>10-40	26,996	173,538	15	2.0 (1.1-3.3)
Gastric bypass				
Follow-up (years)	Cohort (n)	Person-years	Cases (n)	SIR (95%CI)
>1-40	70,176	481,028	17	1.5 (0.9-2.4)
>1-2	70,176	68,506	<4**	0.9 (<0.1-4.9)
>2-5	66,727	183,395	8	2.2 (0.9-4.3)
>5-10	54,791	186,849	7	1.4 (0.6-2.9)
>10-40	16,451	42,278	<4**	0.6 (<0.1-3.6)
Other bariatric procedures ***				
Follow-up (years)	Cohort (n)	Person-years	Cases (n)	SIR (95%CI)
>1-40	21,555	257,474	22	2.6 (1.7-4.0)
>1-2	21,555	20,338	0	-
>2-5	19,126	47,772	4	5.3 (1.4-13.5)
>5-10	13,200	58,105	4	3.2 (0.9-8.7)
>10-40	10,545	131,259	14	2.3 (1.3-3.9)

* Gastric bypass, gastroplasty, gastric banding, sleeve gastrectomy, biliopancreatic diversion, and others.

****** Due to privacy regulations numbers below 4 were not allowed to be presented.

*** All bariatric procedures above except for gastric bypass.

Table 3. Hazard ratios (HR) with 95% confidence intervals (CI) of esophageal and/or cardia adenocarcinoma comparing patients who underwent bariatric surgery with non-operated patients with obesity.

	Person-years	Cases	Crude HR (95% CI)	Adjusted HR (95% CI)
Esophageal or cardia adenocarcinoma				
No bariatric surgery	5,151,084	570	1.0 (Reference)	1.0 (Reference)
Any bariatric surgery*	738,502	39	0.5 (0.3-0.6)	0.9 (0.7-1.3)
Gastric bypass	481,028	17	0.3 (0.2-0.5)	0.6 (0.4-1.0)
Other bariatric procedures**	257,474	22	0.7 (0.4-1.1)	1.6 (1.0-2.6)
Esophageal adenocarcinoma				
No bariatric surgery	5,151084	274	1.0 (Reference)	1.0 (Reference)
Any bariatric surgery*	738,502	16	0.4 (0.2-0.6)	0.8 (0.5-1.3)
Gastric bypass	481,028	4	0.2 (0.1-0.4)	0.3 (0.1-0.8)
Other bariatric procedures**	257,474	12	0.8 (0.4-1.4)	1.8 (1.0-3.4)
Cardia adenocarcinoma				
No bariatric surgery	5,151084	296	1.0 (Reference)	1.0 (Reference)
Any bariatric surgery*	738,502	23	0.5 (0.4-0.8)	1.1 (0.7-1.7)
Gastric bypass	481,028	13	0.5 (0.3-0.9)	0.9 (0.5-1.6)
Other bariatric procedures**	257,474	10	0.6 (0.3-1.2)	1.4 (0.7-2.8)

* Gastric bypass, gastroplasty, gastric banding, sleeve gastrectomy, biliopancreatic diversion, and others.

** All bariatric procedures above except for gastric bypass.

Table 4. Hazard ratios (HR) with 95% confidence intervals (CI) of esophageal or cardia adenocarcinoma comparing patients who underwent bariatric surgery with non-operated patients with obesity, stratified by follow-up periods.

	No bariatric surgery		Gastric bypass		Other bariatric procedures*	
Follow-up (years)	**Cases (n)**	**HR (95% CI)**	**Cases (n)**	**HR (95% CI)**	**Cases (n)**	**HR (95% CI)**
>1-2	56	1.0 (Reference)	<4**	-	0	-
>2-5	178	1.0 (Reference)	8	0.7 (0.3-1.4)	4	1.6 (0.6-4.2)
>5-10	195	1.0 (Reference)	7	0.6 (0.3-1.3)	4	1.3 (0.5-3.6)
>10-40	141	1.0 (Reference)	<4**	0.5 (0.1-3.3)	14	1.9 (1.0-3.4)

* Gastroplasty, gastric banding, sleeve gastrectomy, biliopancreatic diversion, and others.

** Due to privacy regulations numbers below 4 were not allowed to be presented.

Supplementary Tables

Supplementary Table 1. Diagnosis codes defining obesity according to the International Classification of Diseases (ICD) versions 8-10.

	ICD-8	ICD-9	ICD-10
Denmark, Finland, and Sweden	277		E66
Sweden		278A, 278B	
Finland		2780, 2781	

Supplementary Table 2. Bariatric surgery procedures.

Procedure	Number (%)
Gastric bypass	70,176 (76,5%)
Gastroplasty	6,076 (6,6%)
Gastric banding	5,228 (5,7%)
Sleeve gastrectomy	1,209 (1,3%)
Biliopancreatic diversion	506 (0,6%)
Unspecified/other	8,536 (9,3%)

Supplementary Table 3. Procedural codes defining bariatric surgery.

	Denmark, Finland, and Sweden, from year 1997 onwards	Sweden, from 1980 to 1996	Finland, from 1965 to 1996
Bariatric procedures except for gastric bypass	JDF00, JDF01, JDF20, JDF21, JDF32, JDF41, JDF96, JDF97, JDF98, JFD03, JFD04,	4750, 4751, 4753, 4759	6548, 6559
Gastric bypass	JDF10, JDF11	4752	

Supplementary Table 4. Diagnosis codes defining esophageal and cardia adenocarcinoma according to the International Classification of Diseases (ICD).

Site		
	Esophagus	**Cardia**

ICD-7	150	151.1
ICD-10/-O2/-O3	C15	C16.0

Histology	**Adenocarcinoma**	**Adenocarcinoma**
PAD	096	096
ICD-O2/-03 (SNOMED)	814*3	814*3 84803 84903
ICD-10 (SNOMED)	814*3	814*3 84803 84903

Supplementary Table 5. Hazard ratios (HR) with 95% confidence intervals (CI) of esophageal and cardia adenocarcinoma comparing patients who underwent bariatric surgery with non-operated patients with obesity in stratified analyses.

	Person-years	**Cases (number)**	**Adjusted HR (95% CI)**
Sex			
Male			
No bariatric surgery	1,654,927	454	1.0 (Reference)
Gastric bypass	116,871	11	0.6 (0.3-1.0)
Other bariatric surgery *	57,031	17	1.9 (1.2-3.2)
Female			
No bariatric surgery	3,496,157	116	1.0 (Reference)
Gastric bypass	364,157	5	0.7 (0.3-1.6)
Other bariatric surgery *	200,443	6	1.1 (0.4-2.6)
Age at entry (years)			
≤44			
No bariatric surgery	2,476,745	37	1.0 (Reference)
Gastric bypass	284,411	0	-
Other bariatric surgery *	168,283	7	1.9 (0.8-4.3)
>44			
No bariatric surgery	2,674,338	533	1.0 (Reference)
Gastric bypass	196,617	17	0.8 (0.5-1.2)
Other bariatric surgery *	8,9191	15	1.5 (0.9-2.6)
Calendar period at entry			
≤2012			
No bariatric surgery	4,077,754	465	1.0 (Reference)
Gastric bypass	340,917	12	0.6 (0.3-1.1)
Other bariatric surgery *	234,710	18	1.5 (0.9-2.4)
>2012			
No bariatric surgery	1,073,330	105	1.0 (Reference)

Gastric bypass	140,111	5	0.6 (0.3-1.5)
Other bariatric surgery *	22,764	4	3.0 (1.1-8.2)
Country			
Denmark			
No bariatric surgery	2,461,919	285	1.0 (Reference)
Gastric bypass	118,210	<4**	0.1 (<0.1-1.0)
Other bariatric surgery *	15,752	<4**	0.8 (0.1-5.5)
Finland			
No bariatric surgery	960,740	104	1.0 (Reference)
Gastric bypass	29898	<4**	0.4 (0.1-2.7)
Other bariatric surgery *	17,530	<4**	2.1 (0.7-6.6)
Sweden			
No bariatric surgery	1,728,425	181	1.0 (Reference)
Gastric bypass	332,920	15	0.8 (0.5-1.4)
Other bariatric surgery *	224,192	18	1.7 (1.0-2.9)
Charlson comorbidity index			
0			
No bariatric surgery	2,690,504	174	1.0 (Reference)
Gastric bypass	275,376	7	0.6 (0.3-1.2)
Other bariatric surgery *	163,634	12	1.6 (0.9-2.9)
≥1			
No bariatric surgery	2,460,580	396	1.0 (Reference)
Gastric bypass	205,652	10	0.6 (0.3-1.2)
Other bariatric surgery *	93,840	10	1.7 (0.9-3.2)

* Gastroplasty, gastric banding, sleeve gastrectomy, biliopancreatic diversion and unspecified or other.

** Due to privacy regulations numbers blow 4 were not allowed to be presented.