

Risk of Adenocarcinomas of the Esophagus and Gastric Cardia in Patients With Gastroesophageal Reflux Diseases and After Antireflux Surgery

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See editorial on page 1506.

Background & Aims: Gastroesophageal reflux has been proposed as an important risk factor for esophageal and gastric cardia adenocarcinoma, but prospective data are lacking. Furthermore, the effect of antireflux surgery has not yet been studied. We conducted a population-based retrospective cohort study to fill these gaps. **Methods:** A cohort of 35,274 male and 31,691 female patients with a discharge diagnosis of gastroesophageal reflux diseases, and another cohort of 6406 male and 4671 female patients who underwent antireflux surgery, were identified in the Swedish Inpatient Register. Follow-up was attained through record linkage with several nationwide registers. Standardized incidence ratio (SIR) was used to estimate relative risk of upper gastrointestinal cancers, using the general Swedish population as reference. **Results:** After exclusion of the first year follow-up, 37 esophageal and 36 gastric cardia adenocarcinomas were observed among male patients who did not have surgery (SIR, 6.3, 95% confidence interval [CI], 4.5–8.7; SIR, 2.4, 95% CI, 1.7–3.3, respectively). SIR for esophageal adenocarcinoma increased with follow-up time ($P = 0.03$ for trend). Among male patients who had undergone antireflux surgeries, risks were also elevated (16 esophageal adenocarcinoma, SIR, 14.1, 95% CI, 8.0–22.8; 15 gastric cardia adenocarcinomas, SIR, 5.3, 95% CI, 3.0–8.7) and remained elevated with time after surgery. The cancer risk pattern in women was similar to that for men, but the number of cases were much smaller. **Conclusions:** Gastroesophageal reflux is strongly associated with the risk of esophageal adenocarcinoma, and to a lesser extent, with gastric cardia adenocarcinoma. The risk of developing adenocarcinomas of the esophagus and gastric cardia remains increased after antireflux surgery.

Rapid increases in the incidence of adenocarcinomas of the esophagus and gastric cardia have been reported in the United States, Sweden, and other western European countries, and the upward trend persists into

the 1990s.^{1–5} Case–control studies have implicated gastroesophageal reflux as an important risk factor.^{6–8} However, this possible causal relationship has not yet been confirmed in prospective studies. Such confirmation is important because recall bias may be suspected in case–control studies.

Antireflux surgery can successfully prevent gastroesophageal reflux by restoring function of the incompetent antireflux barrier.⁹ However, occurrence of esophageal adenocarcinoma after successful operations has been observed in several small clinical studies.^{10–12} Epidemiologic studies have not yet elucidated whether antireflux surgery may moderate the risk of adenocarcinomas of the esophagus and gastric cardia among patients with gastroesophageal reflux.

To quantify the risk of adenocarcinomas of the esophagus and gastric cardia in relationship to gastroesophageal reflux and antireflux surgery, we conducted a nationwide population-based retrospective cohort study in Sweden among patients hospitalized for heartburn, hiatal hernia, or esophagitis, the diagnoses typically used for gastroesophageal reflux, and patients undergoing antireflux surgery.

Methods

Inpatient Register

In 1964–1965, with computerization of discharge records for patients hospitalized in Sweden, the National Board of Health and Welfare established the Swedish Inpatient Register. In addition to the patients' national registration number (a unique identification number assigned to every resident in Sweden) up to 6 discharge diagnoses and 6 surgical procedures were included for each hospitalization. The 7th revision of the International Classification of Diseases (ICD-7) was used for

Abbreviations used in this paper: 95% CI, 95% confidence interval; SIR, standardized incidence ratio.

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coding diagnoses through 1968, the 8th revision (ICD-8) for diagnoses between 1969 and 1986, the 9th revision (ICD-9) for diagnoses between 1987 and 1996, and the 10th revision (ICD-10) for diagnoses thereafter. The surgical procedures were coded according to the Swedish Classification of Operations and Major Procedures. The percentage of the Swedish population covered by the Swedish Inpatient Register was 60% in 1969, 85% in 1983, and 100% in 1987 and after. Because there has been virtually no private in-hospital care in Sweden and patients have been obliged to use a hospital in their county of residence, a study based on the Swedish Inpatient Register can be considered population-based.

Using data from 1965 to 1997, we identified 85,526 unique national registration numbers with at least 1 in-hospital episode with a discharge diagnosis of heartburn (ICD-7, 784.30; ICD-8, 784.30; ICD-9, 787B; ICD-10, R12), hiatal hernia (ICD-7, 560.40; ICD-8, 551.30; ICD-9, 553D; ICD-10, K44), or reflux esophagitis (ICD-7, 539.11, 539.12; ICD-8, 530.93, 530.94; ICD-9, 530B, 530C; ICD-10, K20, K21). Of these, 13,198 also had at least one record indicating antireflux surgery (Swedish Classification of Operations and Major Procedures codes: 4270, 4271, 4272; after 1996, JBA, JBB, JBC, JBW). No specific code was available to identify Barrett esophagus.

Follow-up

The national registration numbers enabled record linkage to the National Registry of Causes of Death and the Emigration Register for information on dates of death or emigration. All incident cancers were identified through linkage to the Swedish National Cancer Register, founded in 1958, and 98% complete.¹³ In this register, the percentage of esophageal cancers that were histologically verified exceeded 90% for each year under study and was close to 100% during the last 20 years.^{14–16}

Linkage to the Registers of the Total Population, Death and Emigration identified 169 records with national registration numbers that did not match with those of any living, dead, or emigrated person. These records with incorrect national registration numbers were excluded because they were not available for follow-up and would otherwise contribute only person-time with no risk of cancer or other competing risks. Also deleted were 2455 records with inconsistent or invalid dates uncovered during the record linkage and 7720 records with prevalent cancers. A total of 8217 patients whose only diagnosis of heartburn, hiatal hernia, or esophagitis occurred simultaneously with or after antireflux surgery started follow-up in the antireflux surgery cohort and did not contribute person-time to the unoperated cohort. The final unoperated gastroesophageal reflux cohort included 66,965 patients (35,274 men, 31,691 women) for further analysis.

From the cohort of patients who underwent antireflux surgery, 19 and 363 records were deleted because of incorrect national registration numbers and inconsistent and invalid dates uncovered during the record linkage, respectively. Another 556 records were excluded because of prevalent cancers.

After excluding 1183 patients whose underlying diagnoses for any antireflux surgery did not include heartburn, hiatal hernia, or esophagitis (typically, these patients underwent surgery for anomalies of diaphragm, achalasia and cardiospasm, paraesophageal hernia with obstruction, and so on), a total of 11,077 patients (6406 men and 4671 women) were included in the final antireflux surgery cohort.

Statistical Analysis

Because incidence rates of esophageal and gastric cardia adenocarcinomas were substantially different among men and women, all analyses were stratified by gender. For the cohort of gastroesophageal reflux, person-time was calculated from the date of first recorded hospital discharge with a diagnosis of heartburn, hiatal hernia, or esophagitis until the date of antireflux surgery, first occurrence of any cancer, death, emigration, or the end of observation (December 31, 1997), whichever came first. For the cohort of patients with antireflux procedures, person-time was accumulated from the date of surgery and censored by the same principles as in the gastroesophageal reflux cohort. Cancers first found incidentally at autopsy were excluded from the analyses to avoid possible ascertainment bias. Because the likelihood of being hospitalized with a reflux-related diagnosis may increase if there are also insidious symptoms of a yet undetected cancer, we excluded cancers and person-years accrued during the first year of follow-up to avoid selection bias. Because a separate code for gastric cancer in the cardia was introduced first in 1969, follow-up in the stomach cancer analyses began in 1970.

The standardized incidence ratio (SIR), estimated as the ratio of the observed to the expected number of cancers, was used to estimate relative risk. The expected number of cancers were calculated by multiplying the observed person-time by cancer incidence rates specific for age (in 5-year groups), sex, and calendar year. The expected rates, excluding second primary cancers and cancers first found incidentally at autopsy, were derived from the entire Swedish population and aggregated into 5-year intervals (1965–1969, 1970–1974, 1975–1979, 1980–1984, 1985–1989, 1990–1994, and 1995–1997) to ensure a sufficient number of observations in each cell. The denominator, i.e., person-years at risk, was estimated by the midyear population without previously reported cancer. Because the incidence in the observed cohort was compared with the corresponding incidence in the age-, sex-, and calendar year-matched general population, the SIRs are inherently adjusted for confounding by age at follow-up, sex, and calendar time. Confidence intervals of SIRs were calculated with the assumption that the observed number of events followed a Poisson distribution.¹⁷

Because the validity of the diagnosis may vary with the diagnostic efforts, and perhaps with medical specialty, we stratified the analyses according to whether the diagnosis was preceded by an endoscopic examination and by the type of hospital department. We further stratified according to whether the reflux-related diagnosis was ever a main diagnosis and according to mode of admission (emergency/planned). In Sweden, all inpatient care is scheduled except for care of those

who, for example, have severe forms of gastroesophageal reflux complications and thus require unscheduled (emergency) admission. For the cohort of patients who underwent antireflux surgery, analyses were stratified according to whether a vagotomy was also performed. In both cohorts, analyses were also stratified by follow-up duration and age at entry. The χ^2 test for linear trends was used to evaluate dose-response relationships with age and duration of follow-up.¹⁷

Results

Patients With Gastroesophageal Reflux Who Did Not Undergo Surgery

The cohort included 66,965 patients contributing a total of 376,622 person-years, from which 59,582 person-years accrued during the first year of follow-up were excluded. Demographic and other follow-up data stratified by sex are shown in Table 1. During the first year, we noted 28 cases of esophageal adenocarcinoma (SIR 28.8, 95% CI 19.1–41.6) and 63 cases of gastric cardia adenocarcinoma (SIR 24.3, 95% CI 18.7–31.1) among men, and these tumors were not considered in the subsequent analyses. Among women, 3 esophageal adenocarcinomas (SIR 11.0, 95% CI 2.3–32.2) and 12 gastric cardia adenocarcinomas (SIR 14.5, 95% CI 7.5–25.4) occurred during the first year and were excluded. A total of 2861 patients from the gastroesophageal reflux cohort underwent antireflux surgery later, and they were then moved to the antireflux surgery cohort. The average

duration between the first recorded diagnosis of heartburn, hiatal hernia, or esophagitis and the first antireflux surgery was 1.7 years.

After exclusion of the first-year observation, the incidence rate for esophageal adenocarcinoma among male patients in the unoperated gastroesophageal reflux cohort was 22.4/100,000 person-years. This rendered more than a 6-fold greater risk than in the general population (SIR 6.3, 95% CI 4.5–8.7; Table 2). The excess risk decreased significantly with increasing age at entry into the cohort. The relative risk increased with increasing follow-up time (P for trend = 0.03), with an 11-fold increase in risk at 10 or more years of follow-up (95% CI, 6.0–18.3). To a lesser extent, but still statistically significant, the risk of gastric cardia adenocarcinoma was also elevated (SIR 2.4, 95% CI 1.7–3.3), although the incidence rate (21.8/100,000 person-years) among cohort members was almost identical to that of esophageal adenocarcinoma. Generally significant excess risks were observed in all age groups (age at entry) and follow-up periods, but without apparent trends. A moderately elevated risk was also found for squamous cell carcinoma of the esophagus but not for cancers of the distal stomach (Table 2).

Among women in the gastroesophageal reflux cohort, 10 cases of esophageal adenocarcinomas were diagnosed during 1–32 years of observation, as compared with 1.7 expected, yielding an SIR of 6.1 (95% CI 2.9–11.2). At cancer diagnosis, the female patients were much older

Table 1. Characteristics of the Cohorts of Patients With Gastroesophageal Reflux (Heartburn, Hiatal Hernia, or Esophagitis) and Patients With Antireflux Surgery

Characteristics	Gastroesophageal reflux		Antireflux surgery	
	Men	Women	Men	Women
Number of patients	35,274	31,691	6406	4671
Diagnosis				
Esophagitis never diagnosed				
Heartburn	346	435	21	12
Hiatal hernia	9071	12,216	2860	2545
Esophagitis ever diagnosed	25,857	19,040	3525	2114
Total person-years of follow-up	196,752	179,869	49,403	37,593
Person-years at first year of follow-up	31,279	28,303	6007	4368
Average age at entry (yr)	60.2	66.2	50.0	55.9
Average follow-up (yr)	5.6	5.7	7.7	8.0
Average calendar year at entry	1988	1988	1988	1988
Total number of adenocarcinoma of the esophagus	65	13	23	0
Number of esophageal adenocarcinoma at first year of follow-up	28	3	7	0
Average age at diagnosis of adenocarcinoma of the esophagus after first year of follow-up	70.8	84.6	60.4	—
Total number of adenocarcinoma of the gastric cardia ^a	99	23	18	2
Number of gastric cardia adenocarcinoma at first year of follow-up	63	12	3	0
Average age at diagnosis of adenocarcinoma of the gastric cardia after first year of follow-up	71.7	74.8	68.0	75.4

^aThe starting date of follow-up was 1970, 1 year after the time when the Swedish Cancer Register started to use a specific code (151.1) to indicate cancers located in the gastric cardia. The accumulated person-years in cardia cancer analyses were 194,101 for men and 175,814 for women in the gastroesophageal reflux cohort and 48,615 for men and 36,226 for women in the cohort of antireflux surgery.

Table 2. SIRs and 95% CIs for Cancers of the Esophagus and Stomach Among Male Patients With Heartburn, Hiatal Hernia, or Esophagitis According to Age at Entry and Follow-up Duration

Characteristics	Esophagus						Stomach					
	Adenocarcinoma			Squamous cell carcinoma			Cardia cancer			Noncardia cancer		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Total	37	6.3	4.5–8.7	33	2.1	1.5–3.0	36	2.4	1.7–3.3	65	0.8	0.6–1.0
Age at entry into cohort												
<60 yr	17	10.9	6.3–17.4	10	2.3	1.1–4.2	10	2.6	1.2–4.7	13	0.9	0.5–1.5
60–69 yr	10	5.2	2.5–9.5	15	2.8	1.6–4.7	12	2.5	1.3–4.3	21	0.8	0.5–1.3
≥70 yr	10	4.3	2.1–7.9	8	1.3	0.6–2.6	14	2.2	1.2–3.7	31	0.7	0.5–1.0
P for trend		0.02			0.23			0.71			0.42	
Follow-up												
1–4 yr	13	4.7	2.5–8.1	20	2.6	1.6–4.0	20	2.8	1.7–4.3	29	0.7	0.5–1.0
5–9 yr	10	5.6	2.7–10.2	6	1.2	0.5–2.7	9	1.9	0.9–3.7	26	1.0	0.7–1.5
≥10 yr	14	10.9	6.0–18.3	7	2.2	0.9–4.6	7	2.2	0.9–4.6	10	0.7	0.3–1.2
P for trend		0.03			0.44			0.49			0.66	

Obs, observed number of cancer cases.

(mean 84.6 years, range 78–92 years) than male patients (mean 70.8 years, range 48–82 years). We also observed 11 gastric cardia adenocarcinomas (SIR 2.3, 95% CI 1.1–4.1), 11 esophageal squamous cell carcinomas (SIR 1.5, 95% CI 0.8–2.7), and 34 noncardia stomach cancers (SIR 0.6, 95% CI 0.4–0.9) among women during 1–32 years of observation.

The relative risks for adenocarcinomas of the esophagus and gastric cardia were a little higher among men in whom esophagitis had ever been diagnosed than among

those with only a diagnosis of hiatal hernia, whereas the number of patients hospitalized for heartburn was too small to allow stable estimates (Table 3). Higher relative risks for esophageal adenocarcinoma were also found in male patients who received diagnoses in departments of surgery/otolaryngology, those who had undergone gastroscopy, those whose reflux-related diagnosis was the main diagnosis at least once, or those who had 1 or more emergency admissions for reflux-related diseases. Similar patterns of risk were observed for gastric cardia adeno-

Table 3. SIRs and 95% CIs for Cancers of the Esophagus and Stomach Among Male Patients With Heartburn, Hiatal Hernia, or Esophagitis According to Indicators of Severity and Specificity of Diagnosis

Characteristic	Esophagus						Stomach					
	Adenocarcinoma			Squamous cell carcinoma			Cardia cancer			Noncardia cancer		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Diagnosis												
Esophagitis never diagnosed												
Heartburn	0	—	—	1	7.3	0.2–40.7	0	—	—	0	—	—
Hiatal hernia	11	5.7	2.9–10.3	11	2.0	1.0–3.5	8	1.6	0.7–3.2	25	0.8	0.5–1.2
Esophagitis ever diagnosed	26	6.7	4.4–9.9	21	2.1	1.3–3.2	28	2.8	1.9–4.1	40	0.8	0.6–1.1
GERD diagnosed in departments of surgery or otolaryngology												
No	4	1.6	0.4–4.1	14	2.1	1.1–3.5	9	1.4	0.6–2.6	35	1.0	0.7–1.3
Yes	33	10.0	6.9–14.0	19	2.1	1.3–3.3	27	3.1	2.1–4.6	30	0.6	0.4–0.9
GERD diagnosed by gastroscopy												
No	17	4.7	2.7–7.5	24	2.4	1.6–3.6	23	2.5	1.6–3.7	44	0.8	0.6–1.1
Yes	20	9.1	5.6–14.0	9	1.6	0.7–3.0	13	2.3	1.2–3.9	21	0.7	0.4–1.1
Main diagnosis												
Diseases other than GERD	8	3.3	1.4–6.4	14	2.1	1.2–3.6	9	1.4	0.7–2.7	24	0.7	0.4–1.0
GERD, admitted not as emergency case	9	6.5	3.0–12.3	11	2.9	1.4–5.1	16	4.4	2.5–7.1	12	0.6	0.3–1.1
GERD, admitted at least once as emergency case	20	10.1	6.1–15.5	8	1.5	0.7–3.0	11	2.2	1.1–3.9	29	1.0	0.7–1.5

Obs, observed number of cancer cases; GERD, gastroesophageal reflux diseases, including heartburn, hiatal hernia, or esophagitis.

Table 4. SIRs and 95% CIs for Cancers of the Esophagus and Stomach Among Male Patients With Antireflux Surgery According to Cohort Characteristics

Characteristics	Esophagus						Stomach					
	Adenocarcinoma			Squamous cell carcinoma			Cardia cancer			Noncardia cancer		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Total	16	14.1	8.0–22.8	2	0.7	0.1–2.4	15	5.3	3.0–8.7	10	0.8	0.4–1.4
Age at entry into cohort												
<50 yr	6	33.6	12.3–73.1	0	—	—	1	2.5	0.1–13.0	2	1.6	0.2–5.6
50–59 yr	6	15.2	5.6–33.1	1	0.9	0.02–5.0	6	6.2	2.3–13.4	5	1.3	0.4–3.0
≥60 yr	4	7.1	1.9–18.1	1	0.7	0.02–3.7	8	5.6	2.4–11.0	3	0.4	0.1–1.1
<i>P</i> for trend		0.01			0.77			0.55			0.06	
Follow-up												
1–4 yr	6	16.2	5.9–35.2	0	—	—	7	7.2	2.9–14.9	3	0.7	0.1–2.0
≥5 yr	10	13.0	6.3–24.0	2	1.0	0.1–3.7	8	4.3	1.9–8.4	7	0.8	0.3–1.7
5–9 yr	7	18.5	7.5–38.2	2	2.0	0.2–7.1	5	5.3	1.7–12.4	3	0.7	0.1–2.1
≥10 yr	3	7.7	1.6–22.5	0	—	—	3	3.2	0.7–9.5	4	1.0	0.3–2.5
<i>P</i> for trend		0.32			0.94			0.23			0.64	
Vagotomy												
No	11	11.2	5.6–20.0	2	0.8	0.1–2.8	9	3.7	1.7–7.0	10	0.9	0.4–1.7
Yes	5	32.0	10.4–74.8	0	—	—	6	14.7	5.4–32.0	0	—	—

Obs, observed number of cancer cases.

carcinoma in relation to initial diagnosis, diagnostic department, and whether the condition was a main diagnosis (Table 3). The relative risks for squamous cell carcinoma of the esophagus or cancer of the distal stomach did not vary substantially across groups with the different indices of diagnostic accuracy or severity of reflux mentioned here. The risk pattern in women was similar to that in men for all cancer types studied (data not shown). No material difference was detected when analyses were stratified by calendar year of entry into the cohort (before or after 1987, the year when the Swedish Inpatient Register attained complete nationwide coverage).

Antireflux Surgery Cohort

Compared with patients who did not undergo surgery, those who underwent antireflux surgery were younger when entering the cohort (mean age 50.0 years for men, 55.9 years for women) and were followed up longer (mean follow-up 7.7 years for men, 8.0 years for women; Table 1). Among men, we excluded 6007 person-years and 7 cases of esophageal adenocarcinomas (SIR 78.7, 95% CI 31.6–162.2) and 3 cases of gastric cardia adenocarcinomas (SIR 12.3, 95% CI 2.5–35.9) occurring in the first year of follow-up. During 1–32 years of observation, 16 esophageal adenocarcinoma cases were identified, compared with 1.1 expected cases based on incidence rates for the general Swedish population (SIR 14.1, 95% CI 8.0–22.8; Table 4). The relative risk decreased with increasing age at index operation; the

highest value was observed in those who underwent surgery at ages younger than 50 years (SIR 33.6, 95% CI 12.3–73.1). Patients who underwent vagotomy in addition to the antireflux procedure had a higher relative risk of esophageal adenocarcinoma than those without supplementary vagotomy. The relative risk did not change materially with time after surgery (*P* for trend = 0.32, SIR 7.7, 95% CI 1.6–22.5 for patients followed up for 10 or more years; Table 4). No esophageal adenocarcinoma developed in female patients who underwent antireflux surgery, compared with an expected number of 0.2.

Risk of adenocarcinoma of the gastric cardia was also elevated among men in the antireflux surgery cohort (SIR 5.3, 95% CI 3.0–8.7) based on 15 cases observed during 1–32 years of follow-up (Table 4). There was no trend with age at index operation (*P* = 0.55). Risks decreased with time after surgery, but the trend was not statistically significant (*P* = 0.23). In addition, the risk was higher among patients who had undergone supplementary vagotomy. Among women, only 2 gastric cardia adenocarcinomas were observed during 1–32 years of follow-up, yielding an SIR of 2.7 (95% CI 0.3–9.9). No significant excess risk for esophageal squamous cell carcinoma or cancer of the noncardia stomach was seen in men or women. The risk patterns were similar for all cancer types when cases were further stratified according to entry into the cohort before or after 1987 or when patients who underwent antireflux surgery for reasons

other than gastroesophageal reflux were included in the analysis (data not shown).

Discussion

Our prospective data further strengthen the supposition that the relationship between gastroesophageal reflux disease and esophageal adenocarcinoma is causal. Further support for a causal relationship comes from the higher relative risk of esophageal adenocarcinoma in patients with longer follow-up and in those with indications of more severe gastroesophageal reflux diseases. The moderate excess risk of squamous cell carcinoma of the esophagus in our gastroesophageal reflux patients is in contrast to a previous finding⁷ but consistent with some older data^{18,19} and with reports of esophagitis-like precursor lesions in populations at high risk of esophageal squamous cell carcinoma.²⁰ Misclassification of some adenocarcinoma cases as squamous cell carcinoma could potentially inflate risk estimates for the latter cancer, although such misclassification should be uncommon because these 2 tumor types are easily distinguished by trained pathologists. Strong risk factors for squamous cell carcinoma, notably smoking and alcohol consumption in combination,²¹ may have been overrepresented among patients requiring in-hospital care for gastroesophageal reflux disease, thus explaining the moderately increased risk of squamous cell carcinoma in those patients. Such selection bias is unlikely to have importantly affected the relative risk of esophageal adenocarcinoma because the association of alcohol drinking and smoking with esophageal adenocarcinoma is much weaker.²²

In accordance with findings from our previous case-control study,⁷ we also found a statistically significant, although weaker, association between gastroesophageal reflux and gastric cardia adenocarcinoma. The mechanism for such an association is not clear, because reflux is not indicated in the pathogenesis of intestinal metaplasia of the gastric cardia.²³

Antireflux surgery, if properly done, can successfully control the symptoms and prevent reflux of gastric and duodenal contents with long-term efficacy.^{9,24} Surgery is considered more effective than medical therapy for treatment of complicated gastroesophageal reflux disease.^{25,26} However, because Barrett metaplasia, when it occurs, has typically already developed before surgery is contemplated, there is a scarcity of data on the efficacy of surgery in preventing such metaplasia.²⁷ Moreover, the effect of surgery on already developed metaplasia remains unclear.^{12,28-32} Esophageal or gastric cardia adenocarcinoma have been observed after successful antireflux surgery.¹⁰⁻¹² A previous case-control study suggested no

protective effect, but the analysis in that study was hampered by a small number of patients who had undergone antireflux surgery.⁷

We found no convincing evidence of a protective effect of antireflux surgery against development of adenocarcinomas of the esophagus and gastric cardia because the risks for these tumors remained significantly elevated even 10 or more years after the surgery. There are several possible explanations for the observed risk pattern. One possibility is that the patients selected for surgery generally have more severe reflux diseases, with a higher baseline risk of gastroesophageal adenocarcinoma. Another possible explanation is that the critical carcinogenic events have already occurred before surgery, which tends to be the treatment of last resort. This is supported by our finding that vagotomy in addition to antireflux surgery did not decrease the risk of adenocarcinoma of the esophagus and gastric cardia because vagotomy decreases the acid exposure time. Inhibition of apoptosis in Barrett mucosa, a circumstance that may promote carcinogenesis, remains unchanged after antireflux surgery.³³ Although case series indicate that antireflux surgery in expert hands can have excellent results,³⁴ such surgery in routine hospital care may not always lead to perfect reflux control. Recent experimental data suggest that subtotal control with ensuing acid pulses may lead to increased proliferation and decreased differentiation in Barrett epithelium.^{35,36} Therefore, it is conceivable that suboptimal treatment increases cancer risk. However, we may have overlooked a small long-term protective effect of antireflux surgery; the excess risk of esophageal adenocarcinoma remained relatively stable after the surgery but increased substantially with time among patients who did not undergo surgery. The small number of cases necessitates caution in the interpretation of these results.

Our population-based cohort study design with the largest study size to date and virtually complete follow-up for up to 32 years are strengths of this study. Still, several limitations should be noted. First, in the Swedish Inpatient Register, no data on endoscopic findings or medical treatment are available. Thus we cannot estimate the effect of medical treatment among patients who do not undergo surgery or separate patients with and without Barrett esophagus. Second, information on potential confounders, such as body mass and smoking,³⁷⁻⁴⁰ was not available. However, the excess risk for lung cancer, which was strongly linked to smoking, was small (SIR 1.2, 95% CI 1.0-1.3), suggesting that smokers were only moderately over-represented in our cohort.

Therefore, confounding by smoking is unlikely to explain the strong excess risk of esophageal and gastric cardia adenocarcinoma. The small number (1017) of cohort members with a concurrent diagnosis of obesity precluded any evaluation of the importance of this characteristic, but in a case-control study, obesity was not a strong confounder for the association between symptomatic reflux and esophageal adenocarcinoma.⁷ Last, the relatively small number of adenocarcinomas of the esophagus and gastric cardia rendered some estimates unstable, but the results were consistent and highly significant throughout the analyses. The results are robust; the SIR for esophageal adenocarcinoma would remain significantly elevated even with the extreme assumption that 50% of esophageal adenocarcinoma observed would need to be excluded because of misclassification.

Notwithstanding our impressive SIRs, the association between gastroesophageal reflux disease and adenocarcinoma risk is probably underestimated. First, the diagnostic activity associated with the index hospitalization probably revealed some early cancer cases that would otherwise have been diagnosed later. The exclusion of the first year of observation, therefore, leads to a slight underestimation of the incidence during the next few years. Secondly, the prevalence of reflux in the general population, that served as "unexposed" reference, is substantial.⁷ This admixture of high-risk individuals in the unexposed reference group also leads to underestimation of the true reflux-cancer association.

Although our differential results with regard to esophageal and cardia adenocarcinomas are consistent with the findings of a previous case-control study⁷ in which tumor site was carefully assessed, there is probably considerable misclassification of tumor site in the present register-based study. This may be particularly true for cardia cancer, as shown recently,⁴¹ and may lead to both underestimation and overestimation of SIRs for this cancer site. Misclassification of cardia cancer as esophageal would invariably lead to underestimation of the SIRs pertaining to esophageal adenocarcinoma.

In conclusion, our findings provide further strong evidence of a causal relationship between gastroesophageal reflux disease and adenocarcinomas of the esophagus and gastric cardia. The relative risk was equally high or higher in patients who underwent antireflux surgery, suggesting that the protective effect of such surgery, as used in routine health care in Sweden, is limited or possibly absent. Earlier intervention in patients with severe gastroesophageal reflux and close endoscopic surveillance of patients undergoing antireflux surgery may be recommended.

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