Esophageal Adenocarcinoma After Antireflux Surgery in a Cohort Study From the 5 Nordic Countries

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Objective: We aimed to clarify the long-term risk development of EAC after antireflux surgery.

Summary of Background Data: Gastroesophageal reflux disease (GERD) increases EAC risk, but whether antireflux surgery prevents EAC is uncertain.

Methods: Multinational, population-based cohort study including individuals with GERD from all 5 Nordic countries in 1964–2014. First, EAC risk after antireflux surgery in the cohort was compared with the corresponding background population by calculating standardized incidence ratios (SIRs) with 95% confidence intervals (95% CIs). Second, multivariable Cox proportional hazards regression, providing hazard ratios (HRs) with 95% CIs, compared EAC risk in GERD patients with antireflux surgery with those with nonsurgical treatment.

Results: Among 942,071 GERD patients, 48,863 underwent surgery and 893,208 did not. Compared to the corresponding background population, EAC risk did not decrease after antireflux surgery [SIR 4.90 (95% CI 3.62–6.47) 1–<5 years and SIR 4.57 (95% CI 3.44–5.95) ≥15 years after surgery]. Similarly, no decrease was found for patients with severe GERD (esophagitis or Barrett esophagus) after surgery [SIR 6.09 (95% CI 4.39–8.23) 1–<5 years and SIR = 5.27 (95% CI 3.73–7.23) ≥15 years]. The HRs of EAC were stable comparing the surgery group with the nonsurgery group with GERD [HR 1.71 (95% CI 1.26–2.33) 1–<5 years and HR 1.69 (95% CI 1.24–2.30) ≥15 years after treatment], or for severe GERD [HR 1.56 (95% CI 1.11–2.20) 1–<5 years and HR 1.57 (95% CI 1.08–2.26) ≥15 years after treatment].

Conclusions: Surgical treatment of GERD does not seem to reduce EAC risk.

Keywords: esophageal neoplasm, fundoplication, population-based, proton pump inhibitor, risk

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Gastroesophageal reflux disease (GERD), mainly defined by recurrent and troublesome heartburn or regurgitation,[1] is an increasingly common public health concern, affecting 10%–20% of adults in Western populations.[2,3] GERD is strongly associated with the risk of esophageal adenocarcinoma (EAC), particularly in individuals with severe and objectively determined GERD [ie, esophagitis or Barrett esophagus (premalignant metaplasia)].[4,5] EAC is characterized by increasing incidence, treatment causing serious morbidity, and poor prognosis, highlighting the need for preventive measures.[6] If antireflux therapy prevents EAC, it could open new opportunities of prevention; however, this is a topic of controversy, with conflicting and insufficient research findings.[7,8] Antireflux surgery mimics a human model for studies of EAC risk after antireflux therapy because, starting from a defined date, it creates a mechanical and physiological barrier that prevents duodenogastric contents from reaching the esophagus, with good long-term outcomes.[9] However, the existing literature examining the role of antireflux surgery in the prevention of EAC is sparse and hampered by small sample sizes, short and incomplete follow-up, varying control groups, and selection bias attributable to lack of population-based designs.[10] Antireflux medication with proton pump inhibitors is an effective treatment for gastric acidity, but does not hinder the passage of stomach contents to the esophagus.

This large population-based cohort study with long and complete follow-up aimed to clarify whether antireflux surgery reduces EAC risk over time after treatment, and whether any risk reduction is stronger after antireflux surgery compared to nonsurgical treatment.

METHODS

Study Design

This multinational, population-based cohort study was based on information from nationwide health data registries uniquely available from all 5 Nordic countries (ie, Denmark, Finland, Iceland, Norway, and Sweden) during the 50-year study period 1964–2014. The cohort has been described in detail in a cohort profile.[11] The only inclusion criteria into the cohort was a diagnosis of GERD (the only entry criteria) established by a physician and recorded in the national patient registries in the participating countries. The similar structure of the nationwide health data registries in the Nordic countries and

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Study concept and design were done by all authors. Acquisition of data was done by all authors. Analysis and interpretation of data were done by J.M.O., G.S., and J.L. Drafting of the manuscript was done by J.M.O. and J.L. Critical revision of the manuscript for important intellectual content was done by all authors. Statistical analysis was done by G.S. and K.W. Funding was obtained by J.L. Study supervision was done by J.L.

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the use of personal identity codes of each resident in these countries enabled linkages of individuals' information among the registries.[11,12] All required ethical and data permissions were retrieved from the relevant authorities within each country.[11]

The study exposure was surgical treatment for GERD according to procedure codes and diagnosis codes in the patient registries (Supplemental Table 1, Supplemental Digital Content, http://links.lww.com/SLA/B841). The outcome was EAC risk over time after antireflux surgery, recorded with relevant diagnosis codes and histopathologic codes in the cancer registries (Supplemental Table 2, Supplemental Digital Content, http://links.lww.com/SLA/B841). The group with GERD having undergone antireflux surgery and the group with GERD who did not undergo surgery were separately compared with the respective corresponding background population, and also compared with each other, regarding risk development of EAC over time after treatment.

A sub-cohort consisted of patients with more severe and objectively determined GERD, that is, reflux esophagitis or Barrett esophagus. Data regarding covariates were retrieved from the nationwide patient registries and included sex, age, calendar year, chronic obstructive pulmonary disorder (proxy for tobacco smoking), and obesity diagnosis or type 2 diabetes (proxies for obesity). All participants were 18 years or older at the time of the first diagnosis of GERD (entry into the cohort). The study periods varied in the different countries depending on the year of initiation of registration and the date of data retrieval and were 1979–2014 in Denmark; 1968–2014 in Finland; 2000–2013 in Iceland; 2007–2013 in Norway; and 1964–2013 in Sweden.

Data Sources

The patient registries provided codes and dates that represented all diagnoses and surgical procedures from inpatient and specialized outpatient care in each Nordic country, and the date of birth and sex of the patients. These registries reached complete nationwide coverage in 1978 (Denmark), 1967 (Finland), 1999 (Iceland), 1997 (Norway), and 1987 (Sweden). The completeness and validity of the information in the patient registries are high, with positive predictive values of 85%–100% for most diagnoses and operations.[13–15]

The cancer registries provided anatomical and histologic codes for all EACs within each Nordic country. Nationwide cancer registration started in 1943 (Denmark), 1953 (Finland and Norway), 1955 (Iceland), and 1958 (Sweden). The incidence of EAC is similar in the Nordic countries; therefore, only the Swedish Cancer Registry was used to assess the overall incidence of EACs in the general background population. The Nordic cancer registries have been validated in numerous studies.[16–19] The completeness of the data is $\geq$98.2%, and the accuracy of the data is $\geq$93.8%. The causes of death registries and population registries provided date of death for all study participants, with virtually 100% completeness.[12,20]

The Swedish Prescribed Drug Registry provided data regarding dispensed prescription of proton pump inhibitors and histamine2 (H2) receptor antagonists and was used to validate the use of antireflux medication among patients with GERD who did not undergo antireflux surgery. The nationwide registration started in 2005.

Statistical Analysis

Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated to assess EAC risk development over time in patients with GERD who underwent antireflux surgery and patients who did not with that in their corresponding background population. The incidence of EAC in the background population was based on the incidence in the general Swedish population of the same distribution of sex (male or female), age (<50, 50–65, or >65 years), and calendar period (1980–1984, 1985–1999, or 2000–2015) as in the cohort groups with GERD who underwent surgery and those who did not. A patient entered the cohort at the date of first GERD diagnosis. A patient contributed observations (person-years and EACs) to the antireflux surgery group from date of surgery until date of EAC, death, or end of study, whichever came first. A patient contributed observations to the nonsurgical group from date of GERD diagnosis until date of antireflux surgery, EAC, death, or end of study period, whichever came first. The observed number of EACs in the antireflux surgery group, and separately in the nonsurgery group, was divided by the expected number among individuals of the corresponding age, sex, and calendar period and were categorized for total individual time of follow-up into 1 to less than 5 years, 5 to less than 10 years, 10 to less than 15 years, or 15 years or more after antireflux surgery or nonsurgical treatment of GERD. The first year of follow-up was excluded to avoid detection bias and selection bias.

For direct comparison between the antireflux surgery group and the nonsurgery group, person-years and EAC cases were allocated as described above. Multivariable Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% CIs, categorized by total individual time of follow-up in the same categories as presented above. The initial year was excluded to avoid biased detection or selection. The HRs were adjusted for sex (male or female), age at follow-up (<50, 50–65, or >65 years), calendar period of follow-up (1984 or earlier, 1985–1999, or 2000 or later), chronic obstructive pulmonary disorder (yes or no), and obesity or type 2 diabetes (yes or no) diagnosed before the beginning of follow-up.

For validation purposes, all dispensed prescriptions of proton pump inhibitors and H2-receptor antagonists among patients with GERD who did not undergo antireflux surgery in Sweden from 2007 onwards were identified regardless of duration of treatment. The registration started in Sweden in 2005, but 2007 was chosen to accurately assess new treatment episodes and exclude ongoing medication.

All statistical analyses were conducted by an experienced biostatistician (G.S.) according to a predefined study protocol. The statistical analyses were conducted using Stata/MP version 15.1 (StataCorp LLC, College Station, TX).

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RESULTS

Participants

The total GERD cohort included 942,071 patients who were followed up for a maximum of 50 years. The study included 48,863 individuals with GERD who underwent antireflux surgery {median [interquartile range (IQR)] age, 66.0 (58.0–73.0) years} and 893,208 who did not [median (IQR) age, 71.0 (62.0–78.0) years). The group who underwent antireflux surgery included 33,293 with severe GERD. The nonsurgery group included 265,141 with severe GERD. Table 1 presents characteristics of the participants. The median follow-up time was longer in the surgery group (13.6 years; IQR, 9.0–17.4 years) than in the nonsurgery group (5.1 years; IQR, 2.3–10.0 years), but was longer in the nonsurgery sub-cohort with severe GERD (13.4 years; IQR, 9.3–16.9 years). In total, 610,370 person-years were accumulated after surgery and 6,209,931 person-years after GERD diagnosis. Among the patients with GERD in the nonsurgery group for whom data regarding medication were available, 183,699 (92.1%) were recorded users of antireflux medication (proton pump inhibitor or H2-receptor antagonist), and among these,

TABLE 1. Characteristics of Patients With Any or Severe Gastroesophageal Reflux Disease Who Did and Did Not Undergo Antireflux Surgery*

Characteristic	No Antireflux Surgery	Antireflux Surgery
Gastroesophageal reflux disease		
Patients	893,208 (100)	48,863 (100)
Sex		
Male	433,923 (48.6)	27,392 (56.1)
Female	459,285 (51.4)	21,471 (43.9)
Age, yr		
<50	291,259 (32.6)	24,002 (49.1)
50–65	267,398 (29.9)	18,395 (37.6)
>65	334,551 (37.5)	6466 (13.2)
Endoscopic treatment of metaplasia†	142 (0.02)	3 (0.01)
Obesity diagnosis	37,642 (4.2)	2214 (4.5)
Type 2 diabetes	84,463 (9.4)	3921 (8.0)
Chronic obstructive pulmonary disease	74,387 (8.3)	3760 (7.7)
Secondary antireflux surgery	NA	5480 (11.2)
Esophageal adenocarcinoma		
Age at diagnosis, median (IQR), yr	71.0 (62.0–78.0)	66.0 (58.0–73.0)
Sex		
Male	1935 (79.0)	201 (85.5)
Female	515 (21.0)	34 (14.5)
Total	235 (0.5)	2450 (0.3)
Severe gastroesophageal reflux disease		
Patients	265,141 (100)	33,293 (100)
Sex		
Male	146,746 (55.3)	19,129 (57.5)
Female	118,395 (44.7)	14,164 (42.5)
Age, yr		
<50	81,524 (30.7)	16,835 (50.6)
50–65	82,334 (31.1)	12,791 (38.4)
>65	101,283 (38.2)	3667 (11.0)
Endoscopic treatment of metaplasia†	81 (0.03)	1 (<0.01)
Obesity diagnosis	13,323 (5.0)	1559 (4.7)
Type 2 diabetes	32,126 (12.1)	2686 (8.1)
Chronic obstructive pulmonary disease	27,132 (10.2)	2527 (7.6)
Secondary antireflux surgery	NA	3108 (10.1)
Esophageal adenocarcinoma		
Age at diagnosis, median (IQR), yr	70.0 (62.0–78.0)	64.0 (57.0–73.0)
Sex		
Male	1083 (82.1)	162 (84.8)
Female	236 (17.9)	29 (15.2)
Total	1319 (0.5)	191 (0.6)

*Data are presented as number (percentage) of patients unless otherwise indicated.
†Endoscopic treatment after 1996.
IQR indicates interquartile range; NA, not applicable.

165,773 (90.2%) received their first prescription within 3 months before or after the recorded GERD diagnosis. Among patients with severe GERD, 7143 (97.3%) in the nonsurgery group were recorded users of antireflux medication, and 6530 (91.4%) received their first prescription within 3 months before or after the recorded GERD diagnosis. In the antireflux surgery group, 5480 (11.2%) underwent secondary antireflux surgery among patients with any GERD and 3108 (10.3%) among patients with severe GERD. In both the surgery and nonsurgery groups, less than 0.1% underwent endoscopic treatment against metaplasia (Table 1).

Antireflux Surgery Group Versus Background Population

Among patients who had undergone antireflux surgery, 235 new cases (0.5%) of EAC were identified during follow-up. The SIRs did not decrease over time. The SIR was 4.90 (95% CI, 3.62–6.47) among patients with 1 to less than 5 years of follow-up after surgery, 4.00 (95% CI, 3.02–5.20) among patients with 5 to less than 10 years of follow-up after surgery, 5.16 (95% CI, 3.97–6.59) among patients with 10 to less than 15 years of follow-up after surgery, and 4.57 (95% CI, 3.44–5.95) among patients with 15 years or more of follow-up after surgery (Table 2).

In the sub-cohort of individuals with severe GERD, 191 EACs occurred after antireflux surgery. The SIRs were slightly higher than those in the total cohort, although the pattern of lack of decreasing SIRs with time after surgery was similar. The SIR was 6.09 (95% CI, 4.39–8.23) among patients with 1 to less than 5 years of follow-up after surgery, 4.55 (95% CI, 3.32–6.09) among patients with 5 to less than 10 years of follow-up after surgery and 5.27 (95% CI, 3.73–7.23) among patients with 15 years or more of follow-up after surgery (Table 2).

Nonsurgery Group With GERD Versus Background Population

In the nonsurgery group with GERD, 2450 cases (0.3%) of EAC were identified. The SIRs were increased and did not decrease with time after diagnosis. The SIR was 2.37 (95% CI, 2.17–2.59) among patients with 1 to less than 5 years of follow-up, 2.11 (95% CI, 1.88–2.36) among patients with 5 to less than 10 years of follow-up, 2.41 (95% CI, 2.08–2.78) among patients with 10 to less than 15 years of follow-up, and 3.07 (95% CI, 2.65–3.54) among patients with 15 years or more of follow-up after the GERD diagnosis (Table 2).

In the sub-cohort of individuals with severe GERD (1319 cases of EAC), the pattern was similar. The SIR was 3.61 (95% CI, 3.19–4.07) among patients with 1 to less than 5 years of follow-up after diagnosis, 3.07 (95% CI, 2.66–3.53) among patients with 5 to less than 10 years of follow-up after diagnosis and was 3.82 (95% CI, 3.19–4.55) among patients with 15 years or more of follow-up after diagnosis (Table 2).

Antireflux Surgery Group Versus Nonsurgery Group With GERD

The analysis of patients with GERD who had undergone antireflux surgery compared with those who had not (reference group) showed that the adjusted HR of EAC was stable over time after antireflux surgery compared to nonsurgical treatment. The HR was 1.71 (95% CI, 1.26–2.33) among patients with 1 to less than 5 years of follow-up, 1.85 (95% CI, 1.37–2.48) among patients with 5 to less than 10 years of follow-up and 1.69 (95% CI, 1.24–2.30) among patients with 15 years or more of follow-up (Table 3). In the sub-cohort with severe GERD, the adjusted HR was 1.56 (95% CI, 1.11–2.20) among patients with 1 to less than 5 years of follow-up, 1.55 (95% CI, 1.11–2.16) among patients with 5 to less than 10 years of follow-up and 1.57 (95% CI, 1.08–2.26) among patients with 15 years or more of follow-up (Table 3).

DISCUSSION

This study found that the increased risk of EAC after antireflux surgery did not decrease over time compared with the corresponding background population even after long follow-up. The risk estimates were stable over time also in the comparison of patients with GERD undergoing surgery with those who did not, indicating a similar association of antireflux therapy with risk of EAC. The

TABLE 2. Risk of Esophageal Adenocarcinoma Among Patients With Any or Severe Gastroesophageal Reflux Disease Who Did or Did Not Undergo Antireflux Surgery Compared With the Background Population

	No Antireflux Surgery				Antireflux surgery			
Follow-up, yr	Total No. of Patients	Person-years	No. With EAC	SIR (95% CI)	Total No. of Patients	Person-years	No. With EAC	SIR (95% CI)
Gastroesophageal reflux disease								
1 to <5	799,129	2,481 993	493	2.37 (2.17–2.59)	47,406	177,894	49	4.90 (3.62–6.47)
5 to <10	454,615	1,609,034	313	2.11 (1.88–2.36)	40,977	181,285	56	4.00 (3.02–5.20)
10 to <15	225,772	767,312	190	2.41 (2.08–2.78)	30,430	118,759	64	5.16 (3.97–6.58)
≥15	94,539	497,140	190	3.07 (2.65–3.54)	16,817	84,298	55	4.57 (3.44–5.95)
Severe gastroesophageal reflux disease								
1 to <5	247,524	828,522	264	3.61 (3.19–4.07)	32,578	123,775	42	6.09 (4.39–8.23)
5 to <10	170,547	661,713	197	3.07 (2.66–3.53)	28,960	128,769	45	4.55 (3.32–6.09)
10 to <15	97,698	346,784	116	3.10 (2.56–3.72)	21,393	82,034	55	6.41 (4.83–8.35)
≥15	46,171	259,955	128	3.82 (3.19–4.55)	11,146	49,984	38	5.27 (3.73–7.23)

CI indicates confidence interval; EAC, esophageal adenocarcinoma; SIR, standardized incidence ratio.

patterns were similar in analyses restricted to patients with severe (objectively verified) GERD.

Two smaller population-based studies found no decreased risk of EAC after antireflux surgery compared with the background population, which is an agreement with the present study.[7,8,10] However, the earlier studies had few cases of EAC in the categories of longer follow-up, providing imprecise risk estimates, whereas the current study was the first that well powered to provide robust risk estimates.[7,8,10] Because one of these studies included some of the Swedish participants in the present study,[7] we conducted an analysis excluding these participants, which showed similar results (data not shown). Similar to the findings of the present study, 3 previous meta-analyses did not find a superior reduction in risk of EAC associated with antireflux surgery compared with antireflux medication among patients with GERD or among patients with Barrett esophagus.[10,21,22]

The higher risk estimates of EAC after antireflux surgery compared with nonsurgical treatment among patients with GERD are probably explained by patients who are selected for antireflux surgery having more severe and longer duration of GERD before treatment and therefore having a higher risk of EAC at baseline. When comparing the surgery and nonsurgery groups with GERD, the patients who underwent surgery remained at an elevated but stable increased risk, indicating that none of the groups had any decreasing risk of developing EAC over time after treatment.

Both chronic acid and bile exposure induce cellular damage to the esophageal epithelium, causing EAC.[4,5,23–26] Therefore, it is plausible that effective antireflux treatment, by mechanical prevention of the reflux (antireflux surgery) or reduction of the acidity (medication), would prevent this tumor. Because reflux of bile salts occurs more often among patients with Barrett esophagus compared with patients without Barrett esophagus, antireflux surgery might be more effective in preventing tumor progression. However, some studies have found that proton pump inhibitors also effectively reduce gastroduodenal reflux and bile exposure.[27–32] Yet, no preventive effects of antireflux surgery or medication were found in this study.

The lack of any time-dependent decreasing risk of EAC after antireflux surgery or nonsurgical treatment over time compared with the risk of this tumor in the general population suggest that antireflux therapy does not decrease the risk of EAC, at least not as these treatments are currently used in clinical practice. In the clinical decision-making in the treatment of GERD, several aspects need to be considered, particularly the symptoms of GERD, but also the risk of mortality, morbidity, and complications. However, the findings of the present study do not support the use of antireflux therapy only in the prevention of tumor development.[9,33,34]

TABLE 3. Risk of Esophageal Adenocarcinoma Among Patients With Any or Severe Gastroesophageal Reflux Disease Who Underwent Antireflux Surgery Compared With Those Who Did Not

	No Antireflux Surgery				Antireflux surgery			
Follow-up, yr	Total No. of Patients	Person-years	No. With EAC	HR (95% CI)*	Total No. of Patients	Person-years	No. With EAC	HR (95% CI)*
Gastroesophageal reflux disease								
1 to <5	799,129	2,481,993	493	1.00 (Reference)	47,406	177,894	49	1.71 (1.26–2.33)
5 to <10	454,615	1,609,034	313	1.00 [Reference]	40,977	181,285	56	1.85 (1.37–2.48)
10 to <15	225,772	767,312	190	1.00 [Reference]	30,430	118,759	64	2.28 (1.71–3.05)
≥15	94,539	497,140	190	1.00 [Reference]	16,817	84,298	55	1.69 (1.24–2.30)
Severe gastroesophageal reflux disease								
1 to <5	247,524	828,522	264	1.00 (Reference)	32,578	123,775	42	1.56 (1.11–2.20)
5 to <10	170,547	661,713	197	1.00 [Reference]	28 960	128,769	45	1.55 (1.11–2.16)
10 to <15	97,698	346,784	116	1.00 [Reference]	21,393	82,034	55	2.22 (1.60–3.09)
≥15	46,171	259,955	128	1.00 [Reference]	11,146	49,984	38	1.57 (1.08–2.26)

*Adjusted for sex, age, calendar period, chronic obstructive pulmonary disorder, and obesity (including type 2 diabetes).
CI indicates confidence interval; EAC, esophageal adenocarcinoma; HR, hazard ratio.

Among the strengths of the present study is the population-based design, mirroring clinical practice, counteracting selection bias, and facilitating generalizability to populations outside the Nordic countries. In addition, the personal identity codes allowed individuals to be traceable within nationwide health data registries, uniquely available in the Nordic countries, which enabled complete and long-term follow-up. An ideal comparison group could have been untreated patients with severe GERD, but these patients are rare and highly selected, but the comparison of patients undergoing antireflux surgery with both a comparable background population and with nonsurgery patients with GERD was critical. Sub-analyses restricted to patients with severe GERD (esophagitis or Barrett esophagus) enabled assessment of patients with objectively verified GERD with a particularly strong association with EAC. Finally, the large sample size and long follow-up made the analyses more robust and precise than previous studies.[7,8] This was crucial for assessing the EAC risk after long-term follow-up after antireflux therapy.

The study has also weaknesses. Selection bias was introduced because antireflux surgery is likely to have been more common in patients with more severe GERD. However, there are no reasons to believe that the stable SIRs and HRs over long periods of follow-up after surgery are explained by selection, and the results restricted to patients with severe GERD did not change this pattern. Confounding is a general concern in observational studies. Potential confounders in this study are risk factors for EAC other than reflux disease (ie, older age, male sex, recent calendar period, obesity, and tobacco smoking).[6] Therefore, the analyses were adjusted for these factors. Because obesity diagnosis was presumed to be under-reported in the registries, type 2 diabetes was added as a proxy for obesity in the adjusted analyses owing to its close association with obesity. This strategy has been shown to make adjustment for obesity more complete.[35,36] Direct information regarding tobacco smoking was not available, but instead chronic obstructive pulmonary disorder was used as a proxy for smoking, which is a valid approach.[36,37] Detection bias and selection bias are threats to the results for the initial follow-up period. Therefore, we excluded the first year of treatment.

Another limitation is the lack of data regarding antireflux medication in the entire cohort. However, in the subset of patients for whom data on medication were available, almost all patients who received a diagnosis of GERD who did not undergo antireflux surgery in Sweden after 2007 were recorded users of potent antireflux medications, and among these, most had started taking this medication around the time of the recording of the GERD diagnosis. However, earlier use of medication and changes in use of medication over time were not possible to assess. A proportion of the patients undergoing antireflux surgery might have recurrence of GERD in a postoperative setting.[38] However, among the Swedish patients included in the current cohort, a limited 17.7% had recurrence requiring long-term medication (14.8%) or additional operation (2.9%).[9] The longer follow-up time in the surgery group than the nonsurgery group with GERD is explained by the increasing prevalence of GERD in combination with the decreasing incidence of antireflux surgery during the study period, resulting in a larger proportion of operated GERD patients in the early part of the study period. There were no specific codes for separating different types of antireflux surgery. However, the main surgical techniques (full and semi-fundoplication) have similar associations with GERD.[39–42] The prevalence of GERD in the Nordic countries is similar to the prevalence in other Western countries but higher than in most developing countries, suggesting that the findings might be generalizable at least to other Western populations.[2,3] Immortal time bias or time-dependency of the exposure should not be major issues because patients were recruited from the date of GERD diagnosis, and not the date of surgery, and all person-time occurring within 1 year of inclusion were excluded.

In conclusion, this all-Nordic, population-based cohort study found no decreasing risk of EAC after antireflux surgery or nonsurgical treatment, compared to the background population even 15 years or more after treatment. The risk of EAC was stable over time after antireflux surgery compared with nonsurgical treatment, supporting the finding that no antireflux treatment is associated with reduced risk of EAC. These results indicate that antireflux surgery is not associated with any reduced risk of EAC in patients with GERD.

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