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Risk of Esophageal Adenocarcinoma After Antireflux Surgery in Patients With Gastroesophageal Reflux Disease in the Nordic Countries

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IMPORTANCE Gastroesophageal reflux disease (GERD) is associated with a strong and severity-dependent increased risk of esophageal adenocarcinoma. Whether antireflux surgery prevents esophageal adenocarcinoma is a matter of uncertainty.

OBJECTIVES To examine whether antireflux surgery is associated with reduced risk of esophageal adenocarcinoma and whether the risk is different between surgically and medically treated patients.

DESIGN, SETTING, AND PARTICIPANTS In this multinational, population-based retrospective cohort study from Denmark, Finland, Iceland, Norway, and Sweden, patients undergoing surgery were followed up for a median of 12.7 years, and a comparison group of patients receiving medication only were followed up for a median of 4.8 years. All patients with a registered diagnosis of GERD (or an associated disorder), including 48 414 individuals undergoing surgery and 894 492 receiving medication only, were included in the study. The study periods varied in the different countries depending on the year of initiation of registration and the date of data retrieval, from January 1, 1964, to December 21, 2014.

EXPOSURES Antireflux surgery for GERD.

MAIN OUTCOMES AND MEASURES The risk of esophageal adenocarcinoma over time after surgery was compared with that in a corresponding background population using standardized incidence ratios (SIRs) with 95% CIs and with patients with GERD who received medication using multivariable Cox proportional hazards regression, providing hazard ratios (HRs) with 95% CIs adjusted for confounders.

RESULTS In this study of 942 906 patients with GERD, 48 414 underwent antireflux surgery (median [interquartile range] age, 66.0 [58.0-73.0] years; 27 161 male [56.1%]) and 894 492 received medication only (median [interquartile range] age, 71.0 [62.0-78.0] years; 434 035 male [48.6%]). Among patients undergoing surgery, 177 developed esophageal adenocarcinoma. Esophageal adenocarcinoma risk decreased in a time-dependent manner after surgery compared with the background population (5 to <10 years after surgery: SIR, 7.63; 95% CI, 5.42-10.43; ≥15 years after surgery: SIR, 1.34; 95% CI, 0.98-1.80). Among patients with more severe and objectively determined GERD, the SIRs were 10.08 (95% CI, 6.98-14.09) at 5 to less than 10 years after surgery and 1.67 (95% CI, 1.15-2.35) at 15 years or more after surgery. The risk of esophageal adenocarcinoma did not change over time in surgical patients compared with patients who received medication only (5 to <10 years after surgery: HR, 2.02; 95% CI, 1.44-2.84; ≥15 years: HR, 1.80; 95% CI, 1.28-2.54). The risk remained stable over time in analyses restricted to severe reflux disease (5 to <10 years after surgery: HR, 1.81; 95% CI, 1.24-2.63; ≥15 years after surgery: HR, 1.69; 95% CI, 1.14-2.51).

CONCLUSIONS AND RELEVANCE Medical and surgical treatment of GERD were associated with a similar reduced esophageal adenocarcinoma risk, with the risk decreasing to the same level as that in the background population over time, supporting the hypothesis that effective treatment of GERD might prevent esophageal adenocarcinoma.

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Supplemental content

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Gastroesophageal reflux disease (GERD), mainly defined by heartburn or regurgitation,[1] is an increasingly common public health concern, affecting 10% to 20% of adults in Western populations.[2,3] GERD is strongly and dose dependently associated with the risk of esophageal adenocarcinoma, particularly in individuals with severe and objectively determined reflux (ie, esophagitis or Barrett esophagus [premalignant metaplasia]).[4,5] Esophageal adenocarcinoma is characterized by increasing incidence, treatment causing serious morbidity, and poor prognosis, highlighting the need for preventive measures.[6] If antireflux therapy with surgery or medication prevents esophageal adenocarcinoma, 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 the risk of esophageal adenocarcinoma after antireflux therapy because, starting from a defined date, it creates a mechanical barrier that prevents duodenogastric contents from reaching the esophagus, with good long-term outcomes.[9] However, the existing literature is sparse, and previous investigations are hampered by small sample sizes, short and incomplete follow-up, varying control groups, and selection bias attributable to the lack of population-based designs.[10] This large population-based cohort study with long and complete follow-up aimed to clarify whether antireflux surgery is associated with reduced risk of esophageal adenocarcinoma using both the background population and patients with GERD receiving only medication as comparison groups.

Key Points

Questions Is treatment of gastroesophageal reflux disease (GERD) associated with decreased risk of esophageal adenocarcinoma, and is there a difference in risk between patients treated with antireflux surgery and those receiving medication only?

Findings This multinational, population-based cohort study included 48 414 individuals who underwent antireflux surgery and 894 492 individuals with GERD treated with medication only in any of the 5 Nordic countries. The risk of esophageal adenocarcinoma decreased over time after antireflux surgery to reach a similar level as that in the background population and was similar when comparing individuals who underwent surgery with those who did not.

Meaning Both antireflux surgery and medication may be associated with decreased risk of esophageal adenocarcinoma in patients with GERD, decreasing to a similar level as that in the background population over time.

Methods

Study Design

This multinational, population-based cohort study (Nordic Antireflux Surgery Cohort) was based on information from nationwide health data registries uniquely available from all 5 Nordic countries (ie, Denmark, Finland, Iceland, Norway, and Sweden). The Nordic Antireflux Surgery Cohort has been described in detail in a cohort profile.[11] The similar structure of the nationwide health data registries in the Nordic countries and the use of personal identity numbers of each resident in the Nordic 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 (The Danish Data Protection Agency; Population Register Centre, National Institute for Health and Welfare, Statistics Finland; The Icelandic Data Protection Authority, The National Bioethics Committee; Regional Ethics Committee, Norway; and Regional Ethics Committee, Sweden).[11]

The study exposure was antireflux surgery for GERD according to procedure codes and diagnosis codes in the patient registries (eTable 1 in the Supplement). The outcome was the risk of developing esophageal adenocarcinoma (including the gastroesophageal junction) over time after antireflux surgery, recorded with relevant diagnosis codes and histopathologic codes in the cancer registries (eTable 2 in the Supplement). Two control groups were used: the background population of individuals with age, sex, and calendar year that corresponded to that of the group having undergone antireflux surgery and patients with GERD who did not undergo antireflux surgery (antireflux medication only). The medication-only patients were identified through diagnosis codes in the patient registries (eTable 1 in the Supplement).

Data on secondary antireflux surgery and endoscopic treatment against metaplasia were retrieved for descriptive purposes. A subcohort was established that consisted of patients with more severe and objectively determined reflux disease (ie, 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 and the first antireflux surgery. The study periods varied in the different countries depending on the year of initiation of registration and the date of data retrieval and were July 1, 1979, to December 31, 2014, in Denmark; January 1, 1968, to December 31, 2014, in Finland; January 1, 2000, to December 31, 2013, in Iceland; January 1, 2007, to December 31, 2013, in Norway; and January 1, 1964, to December 31, 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, as well as 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% to 100% for most diagnoses and operations.[13-15]

The cancer registries provided anatomical and histologic codes for all esophageal adenocarcinomas within each Nordic country. Nationwide registration started in 1943 in Denmark, 1953 in Finland and Norway, 1955 in Iceland, and 1958 in Sweden. The incidence of esophageal adenocarcinoma is similar in the Nordic countries; therefore, only the

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Swedish Cancer Registry was used to assess the overall incidence of esophageal adenocarcinomas in the general background population. The Nordic cancer registries have been validated in numerous studies.[16-19] The completeness of the data is 98.2% or greater, and the accuracy of the data is 93.8% or greater. 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 any dispensed prescription of proton pump inhibitors and histamine$_2$ (H_2) 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% CIs were calculated to compare the risk of esophageal adenocarcinoma in patients who underwent antireflux surgery and patients who received medication only with that in the corresponding background population. The incidence of esophageal adenocarcinoma in the background population was based on the incidence in the general Swedish population of the corresponding sex, age (<50, 50-65, or >65 years), and calendar period (1980-1984, 1985-1999, or 2000-2015). A patient entered the cohort at the date of first GERD diagnosis or at the date of antireflux surgery, whichever came first. A patient contributed observations (person-years and esophageal adenocarcinomas) to the GERD group from date of diagnosis until date of antireflux surgery, date of esophageal adenocarcinoma, date of death, or end of study period, whichever came first. A patient contributed observations to the antireflux surgery group from date of operation until date of esophageal adenocarcinoma, date of death, or end of study, whichever came first. The observed number of esophageal adenocarcinomas in the antireflux surgery group and in the medication-only group was divided by the expected number among individuals of the corresponding age, sex, and calendar period and categorized for total individual time of follow-up into 5 to less than 10 years, 10 to less than 15 years, or 15 years or more after antireflux surgery or reflux disease diagnosis. The first 5 years of follow-up were excluded to counteract detection bias and to include only exposure time long enough to allow the exposure to influence the risk of esophageal adenocarcinoma. To further assess the trends in the risk of developing esophageal adenocarcinoma over time after antireflux surgery and medication, *P* values for trend were determined using Poisson regression. $P < .05$ (2-sided) was considered to indicate statistical significance.

For comparison between the antireflux surgery group and the GERD group, person-years and esophageal adenocarcinoma cases were allocated as described above. Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% CIs, categorized by total individual time of follow-up into 5 to less than 10 years, 10 to less than 15 years, or 15 years or more after antireflux surgery or reflux diagnosis. The initial 5 years were excluded for the reasons stated above. The HRs were adjusted for sex, 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 H_2-receptor antagonists among patients with GERD who did not undergo antireflux surgery in Sweden since 2007 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 (K.W.) according to a predefined study protocol. The statistical analyses were conducted using IBM SPSS Statistics, version 24 (IBM Corp).

Results

Participants

The total GERD cohort included 942 906 patients. The study included 48 414 individuals who underwent antireflux surgery (median [interquartile range (IQR)] age, 66.0 [58.0-73.0] years; 27 161 male [56.1%]) and 894 492 who did not undergo surgery (median [IQR] age, 71.0 [62.0-78.0] years; 459 340 female [51.4%]). The group who underwent antireflux surgery included 30 537 with severe GERD. The group who had not undergone antireflux surgery included 264 543 with severe GERD. **Table 1** presents characteristics of the participants. The median follow-up time was longer in the surgery group (12.7 years; IQR, 7.8-16.9 years) than in the nonsurgery group (4.8 years; IQR, 2.0-9.9 years) but was longer in the nonsurgical subcohort with severe GERD (7.0 years; IQR, 2.4-12.6 years). In total, 617 181 person-years were accumulated after surgery and 6 511 385 person-years after reflux 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 H_2-receptor antagonist), and among these, 165 773 (90.2%) received their first prescription within 3 months before or after the 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 GERD diagnosis. In the antireflux surgery group, 2695 (5.6%) underwent secondary antireflux surgery among patients with any GERD and 2029 (6.6%) 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 vs Background Population

Among patients who had undergone antireflux surgery, 177 new cases (0.4%) of esophageal adenocarcinoma were identified during follow-up. The SIR was high initially after surgery but decreased over time; the SIR was 7.63 (95% CI, 5.42-10.43) among patients with 5 to less than 10 years of follow-up after surgery, 3.64 (95% CI, 2.66-4.85) among patients with 10 to less than 15 years of follow-up after surgery, and 1.34 (95% CI, 0.98-

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1.80) among patients with 15 years or more of follow-up after surgery (*P*<. 001, for trend) (**Table 2**).

In the subcohort of individuals with severe GERD, 149 esophageal adenocarcinomas occurred after antireflux surgery. The SIRs were generally higher than those in the total cohort, although the pattern of decreasing SIRs with time after surgery was similar. The SIR was 10.08 (95% CI, 6.98-14.09) among patients with 5 to less than 10 years of follow-up after surgery and 1.67 (95% CI, 1.15-2.35) among patients with 15 years or more of follow-up after surgery (*P*<.001, for trend) (Table 2).

Antireflux Medication Group vs Background Population

In the group with GERD who did not undergo surgery, 2368 cases (0.3%) of esophageal adenocarcinoma were identified. The SIRs were increased early after diagnosis but decreased with time after diagnosis; the SIR was 2.06 (95% CI, 1.83-2.30) among patients with 5 to less than 10 years of follow-up, 1.56 (95% CI, 1.35-1.81) among patients with 10 to less than 15 years of follow-up, and 0.69 (95% CI, 0.59-0.81) among patients with 15 years or more of follow-up after the GERD diagnosis (*P*<.001, for trend) (Table 2).

In the subcohort of individuals with severe GERD, the SIR among patients with severe GERD (1351 cases of esophageal adenocarcinoma) decreased from 3.90 (95% CI, 3.40-4.45) among patients with 5 to less than 10 years of follow-up after diagnosis to 1.16 (95% CI, 0.97-1.39) among patients with 15 years or more of follow-up after diagnosis (*P*<. 001, for trend) (Table 2).

Antireflux Surgery Group vs Antireflux Medication Group

The analysis of patients with GERD who had undergone antireflux surgery compared with those who did not (reference group) showed that the adjusted HR of esophageal adenocarcinoma was stable over time after antireflux surgery or reflux diagnosis. The HR was 2.02 (95% CI, 1.44-2.84) among patients with 5 to less than 10 years of follow-up and 1.80 (95% CI, 1.28-2.54) among patients with 15 years or more of follow-up (**Table 3**). In the subcohort with severe GERD, the adjusted HR was 1.81 (95% CI, 1.24-2.63) among patients with 5 to less than 10 years of follow-up and 1.69 (95% CI, 1.14-2.51) among patients with 15 years or more of follow-up (Table 3).

Discussion

This study found an increased risk of esophageal adenocarcinoma initially after antireflux surgery and GERD diagnosis (using medication) compared with the background population; the risk decreased over time, approaching the level of that in the background population. The risk estimates were stable over time in the comparison of patients with GERD undergoing operations with those receiving medication only, indicating a similar association of antireflux medication with risk of esophageal adenocarcinoma. The patterns were similar in analyses restricted to patients with severe GERD.

Table 1. Characteristics of Patients With Any or Severe Gastroesophageal Reflux Disease Who Did and Did Not Undergo Antireflux Surgery[a]

Characteristic	No Antireflux Surgery	Antireflux Surgery
Gastroesophageal Reflux Disease		
Patients	894 492 (100)	48 414 (100)
Person-years of follow-up	6 511 385 (100)	617 181 (100)
Sex		
Male	434 035 (48.6)	27 161 (56.1)
Female	459 340 (51.4)	21 253 (43.9)
Age, y		
<50	291 732 (32.6)	23 825 (49.2)
50-65	267 861 (29.9)	18 206 (37.6)
>65	334 899 (37.4)	6383 (13.2)
Endoscopic treatment of metaplasia	602 (0.07)	21 (0.04)
Obesity diagnosis	37 642 (4.2)	1537 (3.2)
Type 2 diabetes	84 463 (9.4)	2444 (5.0)
Chronic obstructive pulmonary disease	74 387 (8.3)	2516 (5.2)
Secondary antireflux surgery	NA	2695 (5.6)
Esophageal adenocarcinoma		
Age at diagnosis, median (IQR), y	71.0 (62.0-78.0)	66.0 (58.0-73.0)
Sex		
Male	1884 (79.6)	153 (86.4)
Female	484 (20.4)	24 (13.6)
Total	2368 (0.3)	177 (0.4)
Severe Gastroesophageal Reflux Disease		
Patients	264 543 (100)	30 537 (100)
Person-years of follow-up	2 496 630 (100)	391 908 (100)
Sex		
Male	146 502 (55.4)	17 756 (58.1)
Female	118 041 (44.6)	12 781 (41.9)
Age, y		
<50	83 419 (31.5)	15 529 (50.9)
50-65	82 703 (31.3)	11 686 (38.3)
>65	98 421 (37.2)	3322 (10.9)
Endoscopic treatment of metaplasia	359 (0.1)	16 (0.05)
Obesity diagnosis	13 186 (5.0)	1079 (3.5)
Type 2 diabetes	31 549 (11.9)	1728 (5.7)
Chronic obstructive pulmonary disease	26 717 (10.1)	1675 (5.5)
Secondary antireflux surgery	NA	2029 (6.6)
Esophageal adenocarcinoma		
Age at diagnosis, median (IQR), y	70.0 (62.0-77.0)	65.0 (58.0-73.0)
Sex		
Male	1125 (83.3)	128 (85.9)
Female	226 (16.7)	21 (14.1)
Total	1351 (0.5)	2029 (6.6)

Abbreviations: IQR, interquartile range; NA, not applicable.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

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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, y	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								
5 to <10	223 842	1 584 369	310	2.06 (1.83-2.30)	10 068	78 288	39	7.63 (5.42-10.43)
10 to <15	127 960	1 566 040	185	1.56 (1.35-1.81)	13 428	168 642	46	3.64 (2.66-4.85)
≥15	104 594	2 339 334	156	0.69 (0.59-0.81)	17 542	350 472	45	1.34 (0.98-1.80)
Severe Gastroesophageal Reflux Disease								
5 to <10	70 790	526 564	216	3.90 (3.40-4.45)	6632	52 547	34	10.08 (6.98-14.09)
10 to <15	50 475	659 050	130	2.02 (1.68-2.39)	9494	119 550	40	4.47 (3.20-6.09)
≥15	48 351	1 106 144	123	1.16 (0.97-1.39)	10 865	210 018	33	1.67 (1.15-2.35)

Abbreviations: EAC, esophageal adenocarcinoma; SIR, standardized incidence ratio.

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, y	Total No. of Patients	Person-years	No. With EAC	HR (95% CI)[a]	Total No. of Patients	Person-years	No. With EAC	HR (95% CI)[a]
Gastroesophageal Reflux Disease								
5 to <10	223 842	1 584 369	310	1 [Reference]	10 068	78 288	39	2.02 (1.44-2.84)
10 to <15	127 960	1 566 040	185	1 [Reference]	13 428	168 642	46	1.96 (1.41-2.74)
≥15	104 594	2 339 334	156	1 [Reference]	17 542	350 472	45	1.80 (1.28-2.54)
Severe Gastroesophageal Reflux Disease								
5 to <10	70 790	526 564	216	1 [Reference]	6632	52 547	34	1.81 (1.24-2.63)
10 to <15	50 475	659 050	130	1 [Reference]	9494	119 550	40	1.71 (1.18-2.49)
≥15	48 351	1 106 144	123	1 [Reference]	10 865	210 018	33	1.69 (1.14-2.51)

Abbreviations: EAC, esophageal adenocarcinoma; HR, hazard ratio.

[a] Adjusted for sex, age, calendar period, chronic obstructive pulmonary disorder, and obesity (including type 2 diabetes).

Two smaller population-based studies[7,8,10] found no decreased risk of esophageal adenocarcinoma after antireflux surgery compared with the background population. However, the earlier studies[7,8,10] had few cases of esophageal adenocarcinoma in the categories of longer follow-up, providing imprecise risk estimates, whereas the current study was well powered to provide robust risk estimates.

Similar to the findings of the present study, 3 previous meta-analyses[10,21,22] did not find a superior reduction in risk of cancer associated with antireflux surgery compared with antireflux medication among patients with GERD or among patients with Barrett esophagus. The higher risk estimates of esophageal adenocarcinoma after antireflux surgery compared with medication only among patients with GERD are probably explained by patients who are selected for antireflux surgery having more severe and longer duration of GERD before surgery and therefore potentially having a higher risk of esophageal adenocarcinoma at baseline. When comparing the surgery and nonsurgery groups, the patients who underwent surgery remained at an elevated but stable increased risk compared with the patients who did not undergo surgery, indicating that both groups had a similar decreasing risk of developing esophageal adenocarcinoma over time.

Both chronic acid and bile exposure induce cellular damage to the esophageal epithelium, causing esophageal adenocarcinoma.[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), prevents 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[27-32] have found that proton pump inhibitors also effectively reduce gastroduodenal reflux and bile exposure.

The time-dependent decreasing risk of esophageal adenocarcinoma after antireflux surgery or reflux diagnosis (with initiation of potent medical treatment) over time compared with the risk of this tumor in the general population suggest validity of the findings of this study (ie, that antireflux therapy is associated with decreased risk of esophageal adenocarcinoma). The high prevalence of GERD and the low incidence of esophageal adenocarcinoma stress the need not to overestimate the role of antireflux therapy for reducing the risk of cancer, but the findings support the use of antireflux therapy in patients at high absolute risk of tumor development (eg, those with Barrett esophagus). In the clinical decision-making in the treatment of GERD, several aspects need to be considered, including the risk of mortality, morbidity, and complications.[9,33,34]

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Strengths and Limitations

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 numbers allowed individuals to be traceable within nationwide health data registries, uniquely available in the Nordic countries, which enabled complete and long-term follow-up. The comparison of patients undergoing antireflux surgery with both a comparable background population and patients with GERD using only antireflux medication was critical. Subanalyses restricted to patients with severe GERD (esophagitis or Barrett esophagus) enabled assessment of patients with objectively verified reflux disease with a particularly strong association with esophageal adenocarcinoma. Finally, the large sample size made the analyses more robust and precise than previous studies.[7,8] The large sample was crucial for assessing the cancer risk after long-term follow-up after antireflux surgery.

Confounding is a general concern in observational studies. Potential confounders in this study are risk factors for esophageal adenocarcinoma 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 underreported 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] 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 with 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 diagnosis. Data regarding changes in use of medication over time were not assessed. A proportion of the patients undergoing antireflux surgery might have recurrence of GERD in a postoperative setting.[38] However, among the Swedish patients in the current cohort, a limited 17.7% had recurrence requiring long-term medication (14.8%) or additional operation (2.9%).[9] There were no specific codes for separating different types of antireflux surgery. However, the various main surgical techniques have similar associations with gastroesophageal reflux.[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,[2,3] suggesting that the findings might be generalizable at least to Western populations.

Conclusions

This all-Nordic, population-based cohort study found decreasing risk estimates of esophageal adenocarcinoma after antireflux medication and antireflux surgery, with levels of risk almost the same as that of the background population 15 years or more after treatment. The risk of esophageal adenocarcinoma was stable over time after antireflux surgery compared with medication, indicating that these treatment alternatives may be similarly associated with reduced risk of esophageal adenocarcinoma. These findings support the hypothesis that antireflux medication and antireflux surgery are associated with reduced risk of esophageal adenocarcinoma in patients with GERD.

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