Title

Laryngeal and pharyngeal squamous cell carcinoma after antireflux surgery in the five Nordic countries

Authors

Manar Yanes, MD[1], Giola Santoni, PhD[1], John Maret-Ouda MD, PhD[1,2], Eivind Ness-Jensen, MD, PhD[1,3,4], Martti Färkkilä, MD, PhD[5], Elsebeth Lynge, MD, PhD[6], Eero Pukkala, PhD[7,8], Pål Romundstad, MSc, PhD[3], Laufey Tryggvadóttir, MSc[9,10], My von Euler-Chelpin, PhD[11], Jesper Lagergren, MD, PhD[1,12]

Affiliations

[1] Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

[2] Centre for Clinical Research Sörmland, Uppsala University, Eskilstuna, Sweden

[3] Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim/Levanger, Norway

[4] Medical Department, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway

[5] Clinic of Gastroenterology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[6] Nykøbing Falster Hospital, University of Copenhagen, Denmark

[7] Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland

[8] Faculty of Social Sciences, Tampere University, Tampere, Finland

[9] Icelandic Cancer Registry, Icelandic Cancer Society, Reykjavik, Iceland

[10] Faculty of Medicine, University of Iceland, Reykjavik, Iceland

[11] Department of Public Health, University of Copenhagen, Copenhagen, Denmark

[12] School of Cancer and Pharmaceutical Sciences, King's College London, United Kingdom

Corresponding author

Professor Jesper Lagergren

Address: Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery, Karolinska Institutet, Retzius Street 13a, 4th Floor, 171 77 Stockholm, Sweden.

E-mail: Jesper.Lagergren@ki.se

Phone: +46 8 524 841 50

Author's contribution

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 M.Y., G.S., and J.L. Drafting of the manuscript was done by M.Y. and J.L. Critical revision of the manuscript for important intellectual content was done by all authors. Statistical analysis was done by M.Y. and G.S. Funding was obtained by J.L. Study supervision was done by J.L.

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Conflicts of interest

None.

Keywords

Neoplasm; larynx; pharynx; gastroesophageal reflux disease; fundoplication; Nissen; antireflux medication; proton pump inhibitor.

Mini-Abstract

In a five-country Nordic cohort of 814,230 GERD-patients, those 47,016 who underwent fundoplication had a decreased risk of laryngeal/pharyngeal cancer (HR 0.55, 95% CI 0.38-0.80). The risk of laryngeal cancer was particularly decreased >10 years after surgery (HR 0.23, 95% CI 0.08-0.69). Thus, antireflux surgery may counteract laryngeal/pharyngeal cancer.

Abstract

Objective: To clarify whether antireflux surgery prevents laryngeal and pharyngeal squamous cell carcinoma.

Summary Background Data: Gastroesophageal reflux disease (GERD) seems to increase the risk of laryngeal and pharyngeal squamous cell carcinoma.

Methods: All-Nordic (Denmark, Finland, Iceland, Norway and Sweden) population-based cohort study of adults with documented GERD in 1980-2014. First, cancer risk after antireflux surgery was compared to the expected risk in the corresponding background population by calculating standardized incidence ratios (SIR) with 95% confidence intervals (CI). Second, cancer risk among antireflux surgery patients was compared to non-operated GERD-patients using multivariable Cox regression, providing hazard ratios (HR) with 95% CIs, adjusted for sex, age, calendar period, and diagnoses related to tobacco smoking, obesity, and alcohol overconsumption.

Results: Among 814,230 GERD-patients, 47,016 (5.8%) underwent antireflux surgery. The overall SIRs and HRs of the combined outcome laryngeal or pharyngeal squamous cell carcinoma (n=39) were decreased after antireflux surgery (SIR=0.62 [95% CI 0.44-0.85]) and HR=0.55 [95% CI 0.38-0.80]). The point estimates were further decreased >10 years after antireflux surgery (SIR=0.48 [95% CI 0.26-0.80] and HR=0.47 [95% CI 0.26-0.85]). The risk estimates of laryngeal squamous cell carcinoma were particularly decreased >10 years after antireflux surgery (SIR=0.28 [95% CI 0.08-0.72] and HR=0.23 [95% CI 0.08-0.69]), while no such decrease over time after surgery was found for pharyngeal squamous cell carcinoma. Analyses of patients with severe GERD (reflux esophagitis or Barrett's esophagus) showed similar results.

Conclusions: Antireflux surgery may decrease the risk of laryngeal squamous cell carcinoma and possibly also of pharyngeal squamous cell carcinoma.

Introduction

Gastroesophageal reflux disease (GERD), defined by troublesome and long-lasting symptoms of heartburn or regurgitation, affects approximately 20% of adults in Western populations.[1,2] Long-standing GERD can damage the esophageal mucosa, and cause esophagitis, metaplasia (Barrett's esophagus), and esophageal adenocarcinoma.[3,4] GERD can also lead to more proximal reflux, i.e. reflux reaching the larynx and pharynx, where it might cause mucosal injury, inflammation, and tumor development.[5] Interestingly, the laryngeal and pharyngeal squamous cell epithelium seems to be more susceptible to damage by duodeno-gastric contents than the esophageal squamous cell epithelium.[6] Thus, GERD appears to be associated with an increased risk of laryngeal and pharyngeal squamous cell carcinoma.[5,7–12] GERD-related carcinogenesis in the esophagus depends on the development of Barrett's esophagus as an intermediate step before adenocarcinoma, and is not associated with esophageal squamous cell carcinoma.[13] Laryngeal and pharyngeal squamous cell carcinomas are otherwise mainly associated with tobacco smoking and high consumption of alcohol.[14] New preventive strategies could arise if antireflux treatment prevents GERD-associated cancers. Antireflux surgery is a valuable tool for research purposes in this respect because it anatomically and physiologically hinders or reduces reflux starting from a specific date. Yet, no study has evaluated whether the risk of laryngeal or pharyngeal squamous cell carcinoma decreases after antireflux surgery, which was the aim of the present multi-country and population-based cohort study.

Methods

Study design

This population-based cohort study in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) investigated associations between antireflux surgery in patients with GERD (exposure, defined in Supplementary Table 1) and the risk of laryngeal and pharyngeal squamous cell carcinoma (outcomes, defined in Supplementary Table 2) during the study period 1980 through 2014. We included only squamous cell carcinomas because other histological types are rare and have different etiologies. The risk of laryngeal and pharyngeal squamous cell carcinoma among patients who have undergone antireflux surgery was compared with two groups: 1) the background Nordic population and 2) GERD-patients who did not undergo antireflux surgery.

Nordic Antireflux Surgery Cohort

The cohort, entitled the Nordic Antireflux Surgery Cohort (NordASCo), was created by merging data from well-established nationwide health data registries with a long history in the Nordic countries. This cohort has been described in detail elsewhere.[15] In brief, all cohort participants had a diagnosis of GERD documented in a patient registry in any of the Nordic countries. A sub-cohort only included patients with severe GERD, i.e. those with and objectively defined reflux esophagitis or Barrett's esophagus. The overall study period was from January 1, 1980 to December 31, 2014, but the start and end years differed between the countries. All participants were aged ≥18 and ≤95 years at the time of the first GERD diagnosis. We excluded individuals with laryngeal or pharyngeal squamous cell carcinoma before the diagnosis of GERD. The similarity in structure of the Nordic countries' health data

registries enabled merging of the data into one large cohort. The personal identity numbers of each resident in the Nordic countries allowed correct linkages of individuals' data between registries.[15,16] Ethical and data permissions were retrieved from the relevant authorities within each country.[15]

Data collection

The data for the patients in the GERD cohort came from the nationwide patient registries, cancer registries, and cause of death registries in the Nordic countries. The data for the background population came from the national total population registries and cancer registries. To assess the use of medications in non-operated patients with GERD, we retrieved data from the Swedish Prescribed Drug Registry. These five types of registries are presented below.

The patient registries were used to identify all cohort participants with a documented diagnosis of GERD, including those who underwent an antireflux surgery procedure of fundoplication for GERD, by providing diagnosis codes and surgical procedure codes from in-hospital and specialized out-patient care in each Nordic country. The specific codes used for defining GERD, severe GERD (reflux esophagitis or Barrett's esophagus) and antireflux surgery in the patient registries are presented in Supplementary Table 1. Additional data collected from these registries for the present study were sex, date of birth, and diagnoses associated with tobacco smoking (chronic obstructive pulmonary disease), obesity (obesity diagnosis and diabetes type 2), and alcohol overconsumption (alcohol-associated vitamin B deficiency, liver disease, and pancreatic disease). Complete nationwide coverage of the patient registries was reached in 1967 (Finland), 1978 (Denmark), 1987 (Sweden), 1997

(Norway), and 1999 (Iceland). The data recorded in these registries have high positive predictive values for most diagnoses and surgical procedures.[17–19]

The cancer registries were used to identify participants who developed laryngeal or pharyngeal squamous cell carcinoma (Supplementary Table 2). The collected data included date of cancer diagnosis, histological type and location of the tumor, and age at cancer diagnosis. All Nordic cancer registries have been nationwide since their initiation in 1943 (Denmark), 1953 (Norway), 1953 (Finland), 1955 (Iceland), and 1958 (Sweden). Numerous validation studies have shown high completeness (≥98%) and accuracy (≥94%) of the cancer registration.[20]

The cause of death registries provided death dates with virtually 100% completeness and accuracy.[16–21] These registries enabled censoring of GERD patients in the cohort who died during follow-up.

The registries of the total population combined with the cancer registries provided data on population count and number of laryngeal and pharyngeal squamous cell carcinoma in the general background populations by age, sex and calendar year in each Nordic country.

The Swedish Prescribed Drug Registry provided data on prescriptions of proton pump inhibitors and histamine-2-receptor antagonists, which were used to validate the use of antireflux medication among non-operated patients with GERD. The nationwide registration started in July 1, 2005.

Statistical analysis

Patients in the GERD cohort contributed person-time at risk of laryngeal or pharyngeal squamous cell carcinoma from the date of the first GERD diagnosis or the date of the first antireflux surgery for GERD. The first year of follow-up was excluded to avoid detection bias, i.e. earlier detection of any laryngeal or pharyngeal squamous cell carcinoma because of the GERD diagnosis or the antireflux surgery. Person-time at risk in the antireflux surgery group was accumulated from one year after the date of surgery until the first occurrence of laryngeal or pharyngeal squamous cell carcinoma, death, or end of study period. Person-time at risk in the non-operated group with GERD was accumulated from more than one year after the date of GERD diagnosis until the date of laryngeal or pharyngeal squamous cell carcinoma, death, end of study period, or antireflux surgery. Thus, GERD patients who underwent antireflux surgery during follow-up were censored from the non-operated GERD group at the date of surgery, and included in the antireflux surgery group instead.

Two statistical approaches were used. First, the cancer risk in the antireflux surgery group (and the non-operated GERD group) was compared to the corresponding background population by calculating standardized incidence ratios (SIRs) and 95% confidence intervals (CI). For each group, the observed number of laryngeal or pharyngeal squamous cell carcinoma was divided by the expected number among individuals of the corresponding country, sex (men or women), age (5-year categories), and calendar period (5-year categories)**.** The expected number for each stratum was calculated by multiplying the number of person-years by the respective incidence rate derived from the national cancer registry data. SIRs were computed for the entire follow-up time (>1-34 years) as well as for each of the follow-up categories >1-5, >5-10, and >10 years.

In the second statistical approach, the cancer risk in the antireflux surgery group was compared with that of the non-operated group with GERD. Multivariable Cox regression was used to calculate hazard ratios (HR) and 95% CIs, adjusted for sex (men or women), age (continuous), calendar period (1980-1989, 1990-1999, or 2000-2014), country (Denmark, Finland, Iceland, Norway, or Sweden), chronic obstructive pulmonary disease (yes or no), obesity diagnosis or diabetes mellitus type 2 (yes or no), and alcohol-related diagnoses (yes or no). The overall HR assessed the entire period (>1-34 years), while the follow-up categories of HR were >1-5, >5-10, and >10 years.

We also conducted analyses restricted to patients with severe GERD, i.e. reflux esophagitis or Barrett's esophagus, in which follow-up started from one year after the date of the first severe GERD diagnosis or the date of antireflux surgery for severe GERD. Norwegian GERD patients were excluded from these sub-analyses, because four-character sub-categories of diagnosis codes were not available in the Norwegian patient registry, making it impossible to distinguish severe GERD from any GERD.

In a sensitivity analysis, we evaluated any potential bias from selection or confounding by using the above-mentioned multivariable Cox regression model to assess the risk of colon cancer in the antireflux surgery group compared to the non-operated group with GERD. Colon cancer was analyzed because it is unrelated to GERD and antireflux surgery and is the most common cancer that occurs frequently in both sexes in the Nordic countries.[22]

In order to validate the use of antireflux medication in the non-operated group with GERD, we assessed the use of proton pump inhibitors or histamine-2-receptor antagonists in Swedish patients with GERD from 2007 onwards. Nationwide registration of medications started in July 1, 2005, but this validation started from 2007 to exclude ongoing medication and accurately assess new treatment episodes. Among non-operated cohort participants, 183,699 (92.1%) patients with any GERD and 7,143 (97.3%) with severe GERD had dispensed prescriptions of antireflux medication. Among the patients with such prescriptions, 165,773 (90.2%) patients with any GERD and 6530 (91.4%) with severe GERD obtained their first prescription within 3 months before or after first diagnosis of GERD.

The data management and statistical analyses followed a pre-defined study protocol, and were conducted using IBM SPSS Statistics version 24 (IBM Corp, Armonk, NY, USA).

Results

Study participants

Among all 814,230 cohort participants with GERD, 47,016 (5.8%) underwent antireflux surgery during the study period. The person-years at risk were 556,234 in the antireflux surgery group and 5,020,529 in the non-operated group with GERD. The sub-cohort of patients with severe GERD consisted of 269,656 individuals, including 34,766 (12.9%) who underwent antireflux surgery. Table 1 shows some characteristics of the study participants with GERD who underwent antireflux surgery and not. The proportion of men was greater (56.3%) in the antireflux surgery group than in the non-operated group (48.5%), and the median age at inclusion was lower in the antireflux surgery group (51 years, interquartile range (IQR) 41-59 years) compared to the non-operated GERD group (58 years, IQR 45-70 years). During follow-up, 39 (0.08%) patients in the antireflux surgery group and 699 (0.09%) in the non-operated group with GERD developed laryngeal or pharyngeal squamous cell carcinoma. In the sub-cohort of severe GERD, 28 (0.08%) and 321 (0.13%) patients developed any of these tumors in the antireflux surgery and non-operated groups, respectively.

Operated patients compared with the background population

After antireflux surgery for GERD, the overall SIRs of the combined outcome laryngeal or pharyngeal squamous cell carcinoma was decreased (SIR 0.62, 95% CI 0.44-0.85), and the point estimate was further decreased after >10 years of follow-up (SIR 0.48, 95% CI 0.26-0.80). In a separate analysis of laryngeal squamous cell carcinoma, the overall SIR was 0.65 (95% CI 0.52-1.32), and >10 years after surgery the SIR decreased to 0.28 (95% CI 0.08-0.72)

(Table 2). The overall SIR of pharyngeal squamous cell carcinoma was also decreased (SIR 0.60, 95% CI 0.36-0.93), but the risk estimates did not decrease further with longer follow-up time after antireflux surgery (Table 2). The sub-analysis of individuals with severe GERD revealed similar results (Table 3).

Non-operated patients compared with the background population

In the non-operated group with GERD, the risk of laryngeal or pharyngeal squamous cell carcinoma was similar to that of the corresponding background population (overall SIR 1.00, 95% CI 0.93-1.08, n=699), without differences between the two tumors or over follow-up (Table 2). The sub-analyses of severe GERD showed similar results (Table 3).

Operated compared with non-operated patients

Compared to non-operated patients with GERD, those who had undergone antireflux surgery had a decreased overall adjusted HR of the combined outcome laryngeal or pharyngeal squamous cell carcinoma (HR 0.55, 95% CI 0.38-0.80), and the point estimate was further slightly reduced after >10 years of follow-up (HR 0.47, 95% CI 0.26-0.85) (Table 4). The overall adjusted HR of laryngeal squamous cell carcinoma analyzed separately was decreased after antireflux surgery (HR 0.53, 95% CI 0.31-0.90), and the point estimate was further decreased after >10 years of follow-up (HR 0.23, 95% CI 0.08-0.69) (Table 4). The overall HR of pharyngeal squamous cell carcinoma was also decreased after antireflux surgery (adjusted HR 0.58, 95% CI 0.35-0.96), but the risk estimates did not decrease with longer follow-up (Table 4). In analyses restricted to patients with severe GERD, the results were mainly similar, but the adjusted point estimates for laryngeal squamous cell carcinoma

were further decreased for the overall risk (HR 0.42, 95% CI 0.21-0.83) and for the risk after >10 years of follow-up (HR 0.19, 95% CI 0.05-0.69) (Table 5).

The sensitivity analysis showed no decreased overall risk of colon cancer in patients GERD who had undergone antireflux surgery compared to those not operated (adjusted HR 1.16, 95% CI 1.04-1.30), and the risk was not decreased in any of the follow-up periods (Supplementary Table 3).

Discussion

This study indicates that patients with GERD who have undergone antireflux surgery have a decreased risk of laryngeal and pharyngeal squamous cell carcinoma compared to the corresponding background population and to non-operated patients with GERD (vastly using antireflux medication).

Methodological strengths of this study include the population-based design, encompassing virtually all patients with documented GERD and antireflux surgery in any of the five Nordic countries, making it the largest antireflux surgery cohort available to date. This design counteracted selection bias, allowed complete and long follow-up (up to 34 years), provided a large sample size, and facilitated generalizability. The assessment of patients with objectively determined GERD (reflux esophagitis or Barrett's esophagus) reduced misclassification of GERD, and the similar results indicate validity of the findings. Another advantage was the comparison with both the background population and non-operated patients with GERD, showing similar results.

Possible limitations include residual or unmeasured confounding. The main risk factors for laryngeal and pharyngeal squamous cell carcinoma, tobacco smoking and alcohol abuse,[14] are relevant confounders in this study, because tobacco smoking is a risk factor also for GERD, although modest, and alcohol consumption can precipitate reflux episodes among patients with GERD.[4] Obesity is a risk factor for GERD,[4] but there is no established association between obesity and laryngeal and pharyngeal squamous cell carcinoma.[23] These three potential confounders were adjusted for in the Cox regression analyses.

However, because no information on tobacco smoking and alcohol consumption from the participants was available in the registries, we were left to use diagnoses closely associated with these exposures as proxies. Although this strategy could be questioned, it has been shown to be valid.[24,25] Because obesity is heavily underreported in the registries, we added type 2 diabetes as a proxy due to its strong association with obesity, a method of adjusting for obesity that has been shown to be useful.[25,26] Another limitation is the potential influence of recurrence of GERD following antireflux surgery, which occurred in 17.7% of Swedish participants in the present cohort.[27] However, this bias should only attenuate the risk estimates and counteract time-dependent risk reductions over time after antireflux surgery, and not explain the associations. Sub-classification of types of antireflux surgery was not possible due to lack of specific surgical codes, but the efficacy on GERD is similar across the main antireflux surgery techniques.[28–31] In the Nordic countries, the prevalence of GERD is higher than in most developing countries, but comparable to most other Western countries,[1,2] which suggests that the results could be generalized to Western populations. Finally, despite the large cohort size, the low incidence of laryngeal and pharyngeal squamous cell carcinoma (n=39, 0.08%) reduced the statistical precision, particularly of some sub-group analyses.

The finding of a decreased risk of laryngeal and pharyngeal squamous cell carcinoma following antireflux surgery suggests that such surgery can counteract these tumors in GERD patients as hypothesized. An alternative explanation is biased selection of more healthy and fit individuals for antireflux surgery who may be less prone to be heavy users of tobacco and alcohol, and thus have a lower risk of these tumors than the corresponding background population and non-operated GERD patients. However, the distribution of diagnoses

associated with tobacco smoking and alcohol abuse was similar in GERD patients with and without antireflux surgery, and the results were adjusted for these exposures. Furthermore, the sensitivity analysis of colon cancer, which is unrelated to GERD and antireflux surgery, did not indicate presence of such bias. Additionally, we found no decreased risk of smoking-associated lung cancer over time after antireflux surgery (in manuscript, data not published), and a recent meta-analysis found that GERD increases the risk of laryngeal cancer regardless of history of tobacco smoking and alcohol consumption.[11] Finally, the further decreased point estimates of laryngeal squamous cell carcinoma over time after antireflux surgery are unlikely to be explained by selection bias. No such trend over time was found for pharyngeal squamous cell carcinoma, indicating a need for a more cautious interpretation of the association between antireflux surgery and the risk of this tumor.

Some studies have documented the efficacy of antireflux surgery in the treatment of laryngopharyngeal reflux,[32] but no other study has, to our knowledge, investigated whether antireflux surgery prevents laryngeal or pharyngeal cancer. In the aerodigestive tract, conditions causing chronic and repeated injury and inflammation have been linked to cancer development, e.g. chronic rhinosinusitis and nasopharyngeal carcinoma,[33] esophagitis and esophageal adenocarcinoma,[34,35] inflammatory bowel disease and colorectal cancer,[36] and chronic hepatitis and hepatocellular carcinoma.[37] GERD has been associated with an increased risk of laryngeal and pharyngeal cancer in several studies.[5,7–12] The lack of association between GERD and laryngeal and pharyngeal squamous cell carcinoma in the present study was unexpected, but could be due to a higher rate of tobacco smoking cessation and alcohol intake reduction in patients who received a GERD diagnosis during in-hospitalization or in specialist out-patient care compared to individuals in the general

background population. It is also possible that the frequent use of antireflux medication, which was used in the vast majority of these patients, had some cancer-preventive effects. Moreover, SIRs were dilated towards null association because the high prevalence of persons with GERD diagnosed by general practitioners or other non-specialist out-patient clinics in the general background population were not possible to exclude from the analyses. In vitro, the hypopharyngeal mucosa has shown inflammatory changes similar to the premalignant condition Barrett's esophagus following exposure to duodeno-gastric reflux.[11] The laryngeal and pharyngeal epithelium seems to be particularly vulnerable to inflammatory damage following contact with duodeno-gastric contents, including hydrochloric acid, pepsin, and bile-salts.[6,38–41] Thus, it is plausible that the hindering of acidic and non-acidic duodeno-gastric reflux by antireflux surgery would prevent laryngeal and pharyngeal cancer development, whereas antireflux medication, predominant in non-operated GERD-patients, would be less preventive since it does not hinder duodeno-gastric reflux, but only reduces its acidic component and the activation of pepsin.[42] The findings of the present study support this hypothesis.

Considering the low incidence of laryngeal and pharyngeal squamous cell carcinoma,[43] the findings of the present study do not suggest recommendation of antireflux surgery for only cancer protective reasons even if future research confirms the results. However, the findings may become useful for a limited group of high-risk patients for these tumors, and they contribute to the understanding of tumor etiology and suggest higher efficacy of antireflux surgery than antireflux medication in the treatment of patients with more proximal reflux and regurgitation.

In conclusion, this population-based cohort study with long and complete follow-up encompassing all five Nordic countries suggests that antireflux surgery in GERD patients decreases the risk of laryngeal squamous cell carcinoma and possibly also pharyngeal squamous cell carcinoma. The results from this first study on the topic need confirmation in future research.

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Table 1. Characteristics of patients with gastroesophageal reflux disease having undergone antireflux surgery or not.

Gastroesophageal reflux disease

	No antireflux surgery Number (%)	Antireflux surgery Number (%)
Total		
Patients*	780,546 (100)	47,016 (100)
Person-years of follow-up	5,020,529	556,234
Sex		
Male	378,757 (48.5)	26,478 (56.3)
Female	401,789 (51.5)	20,538 (43.7)
Age at inclusion		
<50 years	256,475 (32.9)	22,095 (47.0)
50-<65 years	237,604 (30.4)	18,226 (38.8)
≥65 years	286,467 (36.7)	6,695 (14.2)
Obesity diagnosis	38,889 (5.0)	2,267 (5.5)
Diabetes mellitus type 2	78,385 (10.0)	3,959 (8.4)
Chronic obstructive pulmonary disease	70,541 (9.0)	3,822 (8.1)
Excessive alcohol consumption	50,355 (6.5)	3,508 (7.5)
Vitamin B deficiency associated with alcohol	2,163 (0.3)	92 (0.2)
Liver and pancreatic disease related to alcohol intake	15,663 (2.0)	718 (1.5)
Laryngeal or pharyngeal squamous cell carcinoma	699 (0.09)[100]	39 (0.08)[100]
Laryngeal squamous cell carcinoma	311 [44.5]	20 [51.3]
Pharyngeal squamous cell carcinoma	388 [55.5]	19 [48.7]

Severe gastroesophageal reflux disease (with reflux esophagitis or Barrett's esophagus)

	No antireflux surgery Number (%)	Antireflux surgery Number (%)
Total		
Patients	242,619 (100)	34,766 (100)
Person-years of follow-up	1,996,651	425,331
Sex		
Male	133,827 (55.2)	20,065 (57.7)
Female	108,792 (44.8)	14,701 (42.3)
Age at inclusion		
<50 years	76,813 (31.7)	16,737 (48.1)
50-<65 years	76,918 (31.7)	13,768 (39.6)
≥65 years	88,888 (36.6)	4,261 (12.3)
Obesity diagnosis	14,267 (5.9)	1,670 (4.8)
Diabetes mellitus type 2	30,649 (12.6)	3,023 (8.7)
Chronic obstructive pulmonary disease	26,906 (11.1)	2,798 (8.0)
Excessive alcohol consumption	23,428 (9.7)	2,824 (8.1)
Vitamin B deficiency associated with alcohol	1,087 (0.4)	69 (0.2)
Liver and pancreatic disease related to alcohol intake	7,678 (3.2)	584 (1.7)
Laryngeal or pharyngeal squamous cell carcinoma	321 (0.13)[100]	28 (0.08)[100]
Laryngeal squamous cell carcinoma	148 [46.1]	12 [42.9]
Pharyngeal squamous cell carcinoma	173 [53.9]	16 [57.1]

* Among the non-operated patients, 13,332 were also included in the operated group after they were censored from the non-operated group at the date of admission to antireflux surgery.

Table 2. Risk of laryngeal and pharyngeal squamous cell carcinoma among patients with gastroesophageal reflux disease having undergone antireflux surgery or not, compared to the risk in a corresponding background population, presented as standardized incidence ratios (SIR) with 95% confidence intervals (95% CI).

No antireflux surgery

			Laryngeal or pharyngeal squamous cell carcinoma		**Laryngeal squamous cell carcinoma**		**Pharyngeal squamous cell carcinoma**	
Follow-up (years)	Total (n)	Person-years	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)
>1-34	780 546	5 020 529	699	1.00 (0.93-1.08)	311	0.94 (0.84-1.05)	388	1.06 (0.96-1.17)
>1-5	780 546	2 410 469	305	1.05 (0.94-1.17)	133	0.95 (0.79-1.12)	172	1.15 (0.98-1.33)
>5-10	438 408	1 534 799	212	0.99 (0.87-1.14)	99	0.99 (0.80-1.20)	113	1.00 (0.83-1.20)
>10	212 641	1 075 262	182	0.95 (0.81-1.09)	79	0.88 (0.70-1.10)	103	1.00 (0.82-1.21)

Antireflux surgery

			Laryngeal or pharyngeal squamous cell carcinoma		**Laryngeal squamous cell carcinoma**		**Pharyngeal squamous cell carcinoma**	
Follow-up (years)	Total (n)	Person-years	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)
>1-34	47 016	556 234	39	0.62 (0.44-0.85)	20	0.65 (0.40-1.00)	19	0.60 (0.36-0.93)
>1-5	47 016	176 353	8	0.54 (0.23-1.07)	5	0.67 (0.22-1.57)	3	0.41 (0.08-1.20)
>5-10	40 649	179 639	17	0.91 (0.53-1.45)	11	1.20 (0.60-2.14)	6	0.63 (0.23-1.37)
>10	30 159	200 242	14	0.48 (0.26-0.80)	4	0.28 (0.08-0.72)	10	0.67 (0.32-1.23)

Table 3. Risk of laryngeal and pharyngeal squamous cell carcinoma among patients with severe gastroesophageal reflux disease (with reflux esophagitis or Barrett's esophagus) having undergone antireflux surgery or not, compared to the risk in a corresponding background population, presented as standardized incidence ratios (SIR) with 95% confidence intervals (95% CI).

No antireflux surgery

			Laryngeal or pharyngeal squamous cell carcinoma		**Laryngeal squamous cell carcinoma**		**Pharyngeal squamous cell carcinoma**	
Follow-up (years)	Total (n)	Person-years	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)
>1-34	242 619	1 996 651	321	1.05 (0.94-1.17)	148	1.00 (0.85-1.18)	173	1.09 (0.94-1.27)
>1-5	242 619	809 131	120	1.09 (0.90-1.30)	55	1.01 (0.76-1.31)	65	1.17 (0.90-1.49)
>5-10	166 098	640 844	94	0.98 (0.79-1.19)	48	1.04 (0.76-1.37)	46	0.92 (0.67-1.23)
>10	93 957	546 676	107	1.08 (0.89-1.31)	45	0.97 (0.71-1.30)	62	1.18 (0.91-1.52)

Antireflux surgery

			Laryngeal or pharyngeal squamous cell carcinoma		**Laryngeal squamous cell carcinoma**		**Pharyngeal squamous cell carcinoma**	
Follow-up (years)	Total (n)	Person-years	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)
>1-34	34 766	425 331	28	0.60 (0.40-0.87)	12	0.54 (0.28-0.94)	16	0.67 (0.38-1.09)
>1-5	34 766	132 336	5	0.47 (0.15-1.09)	2	0.38 (0.04-1.36)	3	0.56 (0.11-1.62)
>5-10	31 086	138 999	11	0.78 (0.39-1.39)	7	1.03 (0.41-2.12)	4	0.54 (0.14-1.39)
>10	23 400	153 996	12	0.56 (0.29-0.98)	3	0.29 (0.06-0.85)	9	0.81 (0.37-1.53)

Table 4. Risk of laryngeal and pharyngeal squamous cell carcinoma among patients with gastroesophageal reflux disease having undergone antireflux surgery or not, presented as hazard ratios (HR) with 95% confidence intervals (CI).

	No antireflux surgery		Antireflux surgery		
Follow-up (years)	Cases (n)	HR (95% CI)	Cases (n)	Crude HR (95% CI)	Adjusted ǂ HR (95% CI)
Laryngeal or pharyngeal squamous cell carcinoma					
>1-34	699	1.00 (Reference)	39	0.48 (0.34-0.66)	0.55 (0.38-0.80)
>1-5	305	1.00 (Reference)	8	0.36 (0.18-0.73)	0.36 (0.16-0.82)
>5-10	212	1.00 (Reference)	17	0.68 (0.41-1.11)	0.92 (0.53-1.60)
>10	182	1.00 (Reference)	14	0.40 (0.23-0.69)	0.47 (0.26-0.85)
Laryngeal squamous cell carcinoma					
>1-34	311	1.00 (Reference)	20	0.55 (0.35-0.87)	0.53 (0.31-0.90)
>1-5	133	1.00 (Reference)	5	0.52 (0.21-1.27)	0.43 (0.15-1.25)
>5-10	99	1.00 (Reference)	11	0.94 (0.51-1.76)	1.17 (0.57-2.41)
>10	79	1.00 (Reference)	4	0.26 (0.10-0.71)	0.23 (0.08-0.69)
Pharyngeal squamous cell carcinoma					
>1-34	388	1.00 (Reference)	19	0.42 (0.26-0.66)	0.58 (0.35-0.96)
>1-5	172	1.00 (Reference)	3	0.24 (0.08-0.75)	0.30 (0.08-1.09)
>5-10	113	1.00 (Reference)	6	0.45 (0.20-1.02)	0.69 (0.29-1.64)
>10	103	1.00 (Reference)	10	0.52 (0.27-0.99)	0.72 (0.36-1.46)

ǂ Adjusted for sex, age (continuous), calendar period, country, chronic obstructive pulmonary disease, obesity (including diabetes mellitus type 2) and history of excessive alcohol consumption.

Table 5. Risk of laryngeal and pharyngeal squamous cell carcinoma among patients with severe gastroesophageal reflux disease (with reflux esophagitis or Barrett's esophagus) having undergone antireflux surgery or not, presented as hazard ratios (HR) with 95% confidence intervals (CI).

	No antireflux surgery		Antireflux surgery		
Follow-up (years)	Cases (n)	HR (95% CI)	Cases (n)	Crude HR (95% CI)	Adjusted ǂ HR (95% CI)
Laryngeal or pharyngeal squamous cell carcinoma					
>1-34	321	1.00 (Reference)	28	0.48 (0.34-0.66)	0.57 (0.37-0.89)
>1-5	120	1.00 (Reference)	5	0.36 (0.18-0.73)	0.29 (0.10-0.83)
>5-10	94	1.00 (Reference)	11	0.68 (0.41-1.11)	1.08 (0.55-2.13)
>10	107	1.00 (Reference)	12	0.40 (0.23-0.69)	0.54 (0.28-1.04)
Laryngeal squamous cell carcinoma					
>1-34	148	1.00 (Reference)	12	0.55 (0.35-0.87)	0.42 (0.21-0.83)
>1-5	55	1.00 (Reference)	2	0.52 (0.21-1.27)	0.23 (0.05-1.14)
>5-10	48	1.00 (Reference)	7	0.94 (0.51-1.76)	1.16 (0.48-2.84)
>10	45	1.00 (Reference)	3	0.26 (0.10-0.71)	0.19 (0.05-0.69)
Pharyngeal squamous cell carcinoma					
>1-34	173	1.00 (Reference)	16	0.42 (0.26-0.66)	0.75 (0.43-1.30)
>1-5	65	1.00 (Reference)	3	0.24 (0.08-0.75)	0.36 (0.09-1.41)
>5-10	46	1.00 (Reference)	4	0.45 (0.20-1.02)	0.98 (0.35-2.77)
>10	62	1.00 (Reference)	9	0.52 (0.27-0.99)	0.95 (0.46-1.98)

ǂ Adjusted for sex, age (continuous), calendar period, country, chronic obstructive pulmonary disease, obesity (including diabetes mellitus type 2) and history of excessive alcohol consumption.

Online only Supplementary Table 1. Codes used to identify the cohort participants with gastroesophageal reflux disease, severe gastroesophageal reflux disease and those having undergone antireflux surgery in the patient registries in the respective Nordic country.

	Sweden	Finland	Denmark	Iceland	Norway
Gastroesophageal reflux disease					
Gastroesophageal reflux disease	ICD-10: K21.9	ICD-10: K21.9	ICD-10: K21.9	ICD-10: K21.9	ICD-10: K21.9
Hiatal hernia	ICD-7: 560.40 ICD-8: 551.30 ICD-9: 553D ICD-10: K44	ICD-7: 560.40 ICD-8: 551.30 ICD-9: 5513A ICD-10: K44	ICD-8: 551.30, 551.39 ICD-70: DK44	ICD-10: K44	ICD-10: K44
Heartburn	ICD-7: 784.30 ICD-8: 784.30 ICD-9: 787B ICD-10: R12	ICD-7: 784.30 ICD-8: 784.30 ICD-9: 7871A ICD-10: R12	ICD-8: 784.39 ICD-10: DR12	ICD-10: R12	ICD-10: R12
Esophagitis	ICD-7: 539.11, 539.12 ICD-8: 530.93, 530.94 ICD-9: 530B, 530C ICD-10: K20, K21.0	ICD-7: 539.11, 539.12 ICD-8: 530.93, 530.94 ICD-9: 5301A, 5301C-D, 5301X ICD-10: K20, K21.0	ICD-8: 530.90 ICD-10: DK20, DK21.0	ICD-10: K20, K21.0	ICD-10: K20, K21.0
Barrett's esophagus	ICD-10: K22.7	ICD-9: 5301B ICD-10: K22.7	ICD-10: DK22.7	ICD-10: 22.7	ICD-10: K22.7
Severe gastroesophageal reflux disease					
Reflux esophagitis	ICD-7: 539.11, 539.12 ICD-8: 530.93, 530.94 ICD-9: 530B, 530C ICD-10: K21.0	ICD-7: 539.11, 539.12 ICD-8: 530.93, 530.94 ICD-9: 5301A, 5301C-D, 5301X ICD-10: K21.0	ICD-8: 530.90 ICD-10: DK21.0	ICD-10: K21.0	ICD-10: K21.0
Barrett's esophagus	ICD-10: K22.7	ICD-9: 5301B ICD-10: K22.7	ICD-10: DK22.7	ICD-10: 22.7	ICD-10: K22.7
Antireflux surgery					
Historical codes prior to 1997	4272	6241, 6242, 6249, 6251, 6259	4054, 4056, 4074, 4076, 4080, 4084		
Antireflux surgery (NOMESCO codes)	JBC00, JBC01	JBC00, JBC01	KJBC00, KJBC01	JBC00, JBC01	JBC00, JBC01
Other surgeries of the diaphragm and due to gastroesophageal reflux disease (NOMESCO codes)	JBW96, JBW97	JBW96, JBW97	KJBW96, KJBW97	JBW96, JBW97	JBW96, JBW97

Online only Supplementary Table 2. Codes used to define laryngeal and pharyngeal squamous cell carcinoma in the cancer registries of all the Nordic countries.

	Laryngeal squamous cell carcinoma	**Pharyngeal squamous cell carcinoma**
Anatomic localization		
ICD-7[ǂ]	161[a]	145[a], 146[a], 147[a], 148[a]
ICD-9[ǂ]	161[a]	146[a], 147[a], 148[a]
ICD-10[ǂ]	C32[a]	C09[a], C10[a], C11[a], C12[a], C13[a]
ICD-O2[ǂ]	C32[a]	C09[a], C10[a], C11[a], C12.9[b], C13[a]
ICD-O3[ǂ]	C32[a]	C09[a], C10[a], C11[a], C12.9[a], C13[a]
Histologic classification		
Swedish pathology code	144, 146	144, 146
ICD-10/-O2/-O3	807*3[c]	807*3[c]

a All with correct first 3 positions
b All with correct first 5 positions
c All with correct first 3 positions and correct 5th position

Online only Supplementary Table 3. Risk of colon cancer, and laryngeal or pharyngeal squamous cell carcinoma among patients with gastroesophageal reflux disease having undergone antireflux surgery or not, presented as hazard ratios (HR) with 95% confidence intervals (CI).

	No antireflux surgery		Antireflux surgery		
Follow-up (years)	Cases (n)	HR (95% CI)	Cases (n)	Crude HR (95% CI)	Adjusted ǂ HR (95% CI)
Colon cancer					
>1-34	5,115	1.00 (Reference)	410	0.71 (0.64-0.79)	1.16 (1.04-1.30)
>1-5	2,517	1.00 (Reference)	72	0.39 (0.31-0.50)	0.85 (0.66-1.10)
>5-10	1,473	1.00 (Reference)	124	0.71 (0.59-0.86)	1.35 (1.10-1.66)
>10	1,125	1.00 (Reference)	214	1.01 (0.87-1.17)	1.22 (1.04-1.43)
Laryngeal or pharyngeal squamous cell carcinoma					
>1-34	699	1.00 (Reference)	39	0.48 (0.34-0.66)	0.55 (0.38-0.80)
>1-5	305	1.00 (Reference)	8	0.36 (0.18-0.73)	0.36 (0.16-0.82)
>5-10	212	1.00 (Reference)	17	0.68 (0.41-1.11)	0.92 (0.53-1.60)
>10	182	1.00 (Reference)	14	0.40 (0.23-0.69)	0.47 (0.26-0.85)
Laryngeal squamous cell carcinoma					
>1-34	311	1.00 (Reference)	20	0.55 (0.35-0.87)	0.53 (0.31-0.90)
>1-5	133	1.00 (Reference)	5	0.52 (0.21-1.27)	0.43 (0.15-1.25)
>5-10	99	1.00 (Reference)	11	0.94 (0.51-1.76)	1.17 (0.57-2.41)
>10	79	1.00 (Reference)	4	0.26 (0.10-0.71)	0.23 (0.08-0.69)
Pharyngeal squamous cell carcinoma					
>1-34	388	1.00 (Reference)	19	0.42 (0.26-0.66)	0.58 (0.35-0.96)
>1-5	172	1.00 (Reference)	3	0.24 (0.08-0.75)	0.30 (0.08-1.09)
>5-10	113	1.00 (Reference)	6	0.45 (0.20-1.02)	0.69 (0.29-1.64)
>10	103	1.00 (Reference)	10	0.52 (0.27-0.99)	0.72 (0.36-1.46)

ǂ Adjusted for sex, age (continuous), calendar period, country, chronic obstructive pulmonary disease, obesity (including diabetes mellitus type 2) and history of excessive alcohol consumption.