European Journal of Cancer 138 (2020) 80–88

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Antireflux surgery and risk of lung cancer by histological type in a multinational cohort study

Manar Yanes [a], Giola Santoni [a], John Maret-Ouda [a,b], Eivind Ness-Jensen [a,c,d], Martti Färkkilä [e], Elsebeth Lynge [f], Bright Nwaru [g,h], Eero Pukkala [i,j], Pål Romundstad [c], Laufey Tryggvadóttir [k,l], My von Euler-Chelpin [m], Jesper Lagergren [a,n,*]

[a] *Upper Gastrointestinal Surgery, Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden*
[b] *Centre for Clinical Research Sörmland, Uppsala University, Eskilstuna, Sweden*
[c] *Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim/Levanger, Norway*
[d] *Medical Department, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway*
[e] *Clinic of Gastroenterology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[f] *Nykøbing Falster Hospital, University of Copenhagen, Denmark*
[g] *Krefting Research Centre, Institute of Medicine, University of Gothenburg, Sweden*
[h] *Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Sweden*
[i] *Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland*
[j] *Faculty of Social Sciences, Tampere University, Tampere, Finland*
[k] *Icelandic Cancer Registry, Icelandic Cancer Society, Reykjavik, Iceland*
[l] *Faculty of Medicine, University of Iceland, Reykjavik, Iceland*
[m] *Department of Public Health, University of Copenhagen, Copenhagen, Denmark*
[n] *School of Cancer and Pharmaceutical Sciences, King's College London, UK*

Received 23 May 2020; received in revised form 4 July 2020; accepted 17 July 2020
Available online 30 August 2020

KEYWORDS
Neoplasm;
Pulmonary;
Bronchus;
GORD;
GERD;
Fundoplication;

Abstract ***Introduction:*** Airway micro-aspiration might contribute to the proposed associations between gastroesophageal reflux disease (GERD) and some lung diseases, including lung cancer. This study aimed to examine the hypothesis that antireflux surgery decreases the risk of small cell carcinoma, squamous cell carcinoma and adenocarcinoma of the lung differently depending on their location in relation to micro-aspiration.
Methods: Population-based cohort study including patients having undergone antireflux surgery during 1980–2014 in Denmark, Finland, Iceland, Norway or Sweden. Patients having

* *Corresponding author*: Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery, Karolinska Institutet, Retzius Street 13a, 4th Floor, 171 77 Stockholm, Sweden.
E-mail address: Jesper.Lagergren@ki.se (J. Lagergren).

https://doi.org/10.1016/j.ejca.2020.07.018

Nissen

undergone antireflux surgery were compared with two groups: 1) the corresponding background population, by calculating standardised incidence ratios (SIRs) with 95% confidence intervals (CIs) and 2) non-operated GERD-patients, by calculating hazard ratios (HRs) with 95% CIs using multivariable Cox regression with adjustment for sex, age, calendar period, country, chronic obstructive pulmonary disease and obesity diagnosis or type 2 diabetes.

Results: Among all 812,617 GERD-patients, 46,996 (5.8%) had undergone antireflux surgery. The SIRs were statistically significantly decreased for small cell carcinoma (SIR = 0.57, 95% CI 0.41–0.77) and squamous cell carcinoma (SIR = 0.75, 95% CI 0.60–0.92), but not for adenocarcinoma of the lung (SIR = 0.90, 95% CI 0.76–1.06). The HRs were also below unity for small cell carcinoma (HR = 0.63, 95% CI 0.44–0.90) and squamous cell carcinoma (HR = 0.80, 95% CI 0.62–1.03), but not for adenocarcinoma of the lung (HR = 1.03, 95% CI 0.84–1.26). Analyses restricted to patients with objective GERD (reflux oesophagitis or Barrett's oesophagus) showed similar results.

Conclusions: This all-Nordic study indicates that patients who undergo antireflux surgery are at decreased risk of small cell carcinoma and squamous cell carcinoma of the lung, but not of adenocarcinoma of the lung.

1. Introduction

Gastroesophageal reflux disease (GERD), characterised by troublesome heartburn or regurgitation or GERD-specific complications, affects 20% of adults in Western countries [1–4]. Reflux of duodenogastric contents might result in micro-aspiration to the airways [5–7], where it can cause lung diseases, i.e. asthma, chronic obstructive pulmonary disease, pneumonia, idiopathic pulmonary fibrosis and bronchiolitis obliterans syndrome [6–10]. Therefore, in addition to the known associations between GERD and cancer of the oesophagus, larynx and pharynx [11–14], an association with lung cancer has been suggested [15–18]. Yet, no study has examined if antireflux therapy counteracts lung cancer. Medication with proton pump inhibitors reduces the acidity of the duodenogastric contents and relieves symptoms of heartburn but does not stop non-acidic reflux, regurgitation or aspiration, why airway symptoms may still persist or arise [19]. Antireflux surgery, on the other hand, accomplishes a barrier to acidic and non-acidic reflux and can reduce asthma symptoms in GERD-patients [20–22] and improve pulmonary function in lung transplantation patients [23–25]. While lung cancer has one of the highest cancer incidences and mortalities worldwide, the incidence of lung cancer in the Nordic countries is among the lowest in Europe [26,27]. The three main histological types of lung cancer, i.e. small cell carcinoma, squamous cell carcinoma and adenocarcinoma, have different etiological, clinical and molecular characteristics, although tobacco smoking is a shared risk factor [28]. Small cell carcinoma and squamous cell carcinoma primarily arise in the central airways, i.e. closer to any aspiration, while adenocarcinoma mostly arise more peripherally [29]. This multinational Nordic study aimed to test the hypothesis that antireflux surgery decreases the risk of small cell carcinoma, squamous cell carcinoma and adenocarcinoma of the lung in GERD-patients, and that this decrease is stronger for small cell carcinoma and squamous cell carcinoma than for adenocarcinoma because of the differences in proximity to aspirated refluxate.

2. Methods

2.1. Design

This was a population-based cohort study based on well-established and nationwide health data registries in the five Nordic countries, i.e. Denmark, Finland, Iceland, Norway and Sweden (alphabetic order). The overall study period was from 1980 through 2014, but with different start and end years in each country. The study separately investigated the risk of small cell carcinoma, squamous cell carcinoma and adenocarcinoma of the lung after antireflux surgery for GERD. Ethical and data permissions were retrieved from all relevant authorities within each country [30].

2.2. Cohorts

The source cohort, entitled the Nordic Antireflux Surgery Cohort (NordASCo), has been presented in detail in a cohort profile [30]. In summary, data were collected from health data registries, i.e. the patient registries, cancer registries and cause of death registries in the Nordic countries. The similarity in the structure of the health data registries in the Nordic countries, combined with the well-established system of the unique personal identity number assigned to each resident in all Nordic countries, allowed linkages of the individuals' data

between the registries and merging of the collected data [30,31].

The patients in the study cohort, who had GERD documented from in-hospital and specialised out-patient care in any of the national patient registries, were between 18 and 95 years of age, and without any lung cancer before the GERD diagnosis. A sub-cohort was restricted to patients with objective GERD, i.e. objectively determined reflux oesophagitis or Barrett's oesophagus (a columnar cell metaplasia preceding oesophageal adenocarcinoma).

The codes defining GERD, objective GERD and antireflux surgery in the patient registries are presented in Supplementary Table 1. While complete nationwide coverage of the patient registries was reached in the 1970s (Finland), 1978 (Denmark), 1987 (Sweden), 1999 (Iceland) and 2008 (Norway), this study started from 1980, from when data on antireflux surgery was available. The data in these registries have high validity with most diagnoses and operations having a positive predictive value close to 100% [32–34]. The diagnosis of GERD has not been separately validated in the Nordic patient registries; however, the diagnosis codes that correspond to reflux oesophagitis and Barrett's oesophagus require confirmation by endoscopy and histology, which should counteract misclassification. Norwegian GERD patients were excluded from the subanalyses of objective GERD because four-character subcategories of diagnosis codes were not available in the Norwegian patient registry.

2.3. Outcomes

The three outcomes, i.e. small cell carcinoma, squamous cell carcinoma and adenocarcinoma of the lung, were identified in the cancer registries by their relevant diagnosis codes (Supplementary Table 2). The cancer registries provided data on tumour topography, morphology and diagnosis date. To reduce misclassification, histological sub-types that were ill-defined, or that potentially represented poor or undifferentiated forms of lung cancer were excluded. All Nordic cancer registries have been nationwide since their initiation in 1943 (Denmark), 1953 (Norway), 1953 (Finland), 1955 (Iceland) and 1958 (Sweden). Validation studies of these registries have consistently shown high completeness (≥98.2%) and accuracy (≥93.8%) [35]. The cancer registries provided data on cancer incidence in the study cohort. Combined with the registries of the total populations, the cancer registries also provided data on population count and number of lung cancers by histological type in the general background populations by age, sex and calendar year in each Nordic country, which enabled calculation of these tumours' incidence rates in the background population.

2.4. Statistical analysis

When calculating person-years at risk, the first year of follow-up was excluded to avoid detection bias, i.e. earlier tumour detection because of the GERD diagnosis or the antireflux surgery. Person-years at risk in the antireflux surgery groups with any GERD or objective GERD were accumulated from 1 year after surgery until the date of any lung cancer, death or end of study period, whichever occurred first. Person-years at risk in the non-operated groups with any GERD or objective GERD were accumulated from 1 year after the date of GERD until the first occurrence of any type of lung cancer, death, end of the study period or the date of admission for antireflux surgery. In this way, GERD patients who underwent antireflux surgery were censored from the non-operated group at the date of admission for antireflux surgery, and 1 year after that date included in the antireflux surgery group instead.

Two statistical approaches were used to calculate the measures of relative risks. The incidence in the cohort was first compared with the incidence of the corresponding background population by calculating standardised incidence ratios (SIRs) and 95% confidence intervals (CIs). The observed number of small cell carcinomas, squamous cell carcinomas or adenocarcinomas of the lung in the patient cohorts was divided by the expected number among individuals of the corresponding sex (male or female), age group (5-year categories) and calendar period (5-year categories). SIRs were computed for the overall period (>1–34 years) and separately for the specific follow-up categories, i.e. >1–5, >5–10, >10–15 and >15 years. It was not possible to exclude the cases of small cell carcinomas, squamous cell carcinomas or adenocarcinomas in the cohort from the background population, but the low incidence of these tumours means that the results would not be much influenced and any influence would dilute estimates rather than contribute to associations.

In the second statistical approach, the risk of lung cancer in the antireflux surgery groups with any GERD and objective GERD were compared with the non-operated groups with any GERD or objective GERD, using the non-operated groups as references. Multivariable Cox regression was used to calculate hazard ratios (HRs) and 95% CIs, adjusted for six potential confounders: sex (male or female), 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) and obesity diagnosis or diabetes mellitus type 2 (yes or no). Chronic obstructive pulmonary disease was used as a marker of tobacco smoking, whereas obesity diagnosis or diabetes mellitus type 2 represented obesity in the models. These conditions are chronic and were thus measured without time restrictions. The follow-up

categories were the same as those described above for the calculation of SIRs, i.e. >1–34, >1–5, >5–10, >10–15 and >15 years. The proportionality hazards assumption was examined by plotting log (-log) survival function versus log analysis time. The assumption was met for small cell carcinoma, but not for squamous cell carcinoma or adenocarcinoma, which was solved by the stratification into follow-up time periods.

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).

3. Results

3.1. Patients

Of all 812,617 cohort patients with any GERD (5,011,842 person-years at risk), 46,996 (5.8%) underwent antireflux surgery (555,748 person-years at risk). Among patients in the non-operated group, 13,332 were censored and included in the antireflux surgery group from the date of admission to antireflux surgery. Of 269,318 patients with objective GERD, 34,752 (12.9%) underwent antireflux surgery (Table 1). Among patients with any GERD, 3650 (0.5%) developed lung cancer during follow-up in the non-operated group and 273 (0.6%) in the operated group. In patients with objective GERD, 1491 (0.6%) and 191 (0.5%) developed lung cancer in the non-operated and operated group, respectively (Table 1).

3.2. Operated patients with gastroesophageal reflux disease compared with the background population

Table 2A shows the SIRs after antireflux surgery for any GERD. The overall SIRs were particularly decreased for small cell carcinoma (SIR 0.57, 95% CI 0.41–0.77) and also for squamous cell carcinoma (SIR 0.75, 95% CI 0.60–0.92), but not for adenocarcinoma of the lung (SIR 0.90, 95% CI 0.76–1.06). The SIRs did not decrease with longer follow-up time after antireflux surgery for any of the three histological types. In the analyses of patients with objective GERD, most estimates were similar to those in the entire GERD cohort (Table 2B).

3.3. Non-operated patients with gastroesophageal reflux disease compared with the background population

The SIRs were lower for small cell carcinoma (SIR 0.83, 95% CI 0.77–0.89), squamous cell carcinoma (SIR 0.87, 95% CI 0.82–0.92) and adenocarcinoma (SIR 0.83, 95% CI 0.80–0.87) (Table 2A). The SIRs did not change much over follow-up periods, and the results were similar for objective GERD (Table 2B).

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

	Antireflux surgery Number (%)	No antireflux surgery Number (%)
Any gastroesophageal reflux disease		
Total		
Patients[a]	46,996 (100)	778,943 (100)
Person-years of follow-up	555,748	5,011,842
Sex		
Male	26,475 (56.3)	378,245 (48.6)
Female	20,521 (43.7)	400,698 (51.4)
Age at inclusion		
<50 years	22,088 (47.0)	256,401 (32.9)
50–<65 years	18,218 (38.8)	237,215 (30.5)
≥65 years	6690 (14.2)	285,327 (36.6)
Chronic obstructive pulmonary disease	3821 (8.1)	69,889 (9.0)
Obesity diagnosis	2267 (4.8)	38,850 (5.0)
Diabetes mellitus type 2	3960 (8.4)	78,221 (10.0)
Lung cancer	273 (0.6) [100]	3650 (0.5) [100]
Small cell carcinoma	43 [15.8]	724 [19.8]
Squamous cell carcinoma	88 [32.2]	1152 [31.6]
Adenocarcinoma	142 [52.0]	1774 [48.6]
Objective gastroesophageal reflux disease (reflux oesophagitis or Barrett's oesophagus)		
Total		
Patients	34,752 (100)	242,292 (100)
Person-years of follow-up	425,008	1,993,691
Sex		
Male	20,063 (57.7)	133,703 (55.2)
Female	14,689 (42.3)	108,589 (44.8)
Age at inclusion		
<50 years	16,731 (48.1)	76,808 (31.7)
50–<65 years	13,758 (39.6)	76,837 (31.7)
≥65 years	4263 (12.3)	88,647 (36.6)
Chronic obstructive pulmonary disease	2797 (8.0)	26,746 (11.0)
Obesity diagnosis	1670 (4.8)	14,248 (5.9)
Diabetes mellitus type 2	3024 (8.7)	30,608 (12.6)
Lung cancer	191 (0.5) [100]	1491 (0.6) [100]
Small cell carcinoma	31 [16.2]	313 [21.0]
Squamous cell carcinoma	59 [30.9]	472 [31.7]
Adenocarcinoma	101 [52.9]	674 [45.2]

[a] Among the non-operated patients, 13,322 were also included in the operated group after they were censored from the non-operated group at the date of admission to antireflux surgery.

3.4. Operated compared with non-operated patients with gastroesophageal reflux disease

Table 3A presents the HRs for the group who had undergone antireflux surgery for any GERD compared with the non-operated group with any GERD. The overall adjusted HRs after antireflux surgery were decreased for small cell carcinoma (HR 0.63, 95% CI 0.44–0.90), decreased without statistical significance for squamous cell carcinoma (HR 0.80, 95% CI 0.62–1.03), and not decreased for adenocarcinoma (HR 1.03, 95% CI 0.84–1.26). The HRs did not decrease over time after antireflux surgery for any of the histological types, but for small cell carcinoma, the point estimates remained

Table 2A
Risk of lung cancer by histological type among patients with any gastroesophageal reflux disease compared with the corresponding background population, presented as standardised incidence ratios (SIRs) with 95% confidence intervals (95% CIs).

			Small cell carcinoma		Squamous cell carcinoma		Adenocarcinoma	
Follow-up (years)	Total (n)	Person-years	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)
Antireflux surgery								
>1–34	46,966	555,748	43	0.57 (0.41–0.77)	88	0.75 (0.60–0.92)	142	0.90 (0.76–1.06)
>1–5	46,966	176,254	14	0.75 (0.41–1.26)	16	0.59 (0.34–0.95)	24	0.74 (0.47–1.09)
>5–10	40,618	179,507	7	0.31 (0.12–0.64)	25	0.73 (0.47–1.08)	42	0.94 (0.68–1.27)
>10–15	30,142	117,401	11	0.62 (0.31–1.11)	19	0.67 (0.40–1.05)	40	1.00 (0.72–1.37)
>15	16,605	82,585	11	0.68 (0.34–1.22)	28	1.00 (0.66–1.44)	36	0.89 (0.62–1.23)
No antireflux surgery								
>1–34	778,943	5,011,842	724	0.83 (0.77–0.89)	1152	0.87 (0.82–0.92)	1774	0.83 (0.80–0.87)
>1–5	778,943	2,406,216	332	0.86 (0.77–0.96)	550	0.95 (0.87–1.03)	786	0.88 (0.82–0.94)
>5–10	437,681	1,532,301	200	0.77 (0.67–0.89)	322	0.81 (0.73–0.91)	562	0.87 (0.80–0.95)
>10–15	212,288	707,015	114	0.82 (0.67–0.98)	160	0.76 (0.64–0.88)	274	0.76 (0.68–0.86)
>15	83,989	366,310	78	0.88 (0.69–1.10)	120	0.87 (0.72–1.04)	152	0.67 (0.57–0.79)

Table 2B
Risk of lung cancer by histological type among patients with objective gastroesophageal reflux disease (reflux oesophagitis or Barrett's oesophagus) compared to the corresponding background population, presented as standardised incidence ratios (SIRs) with 95% confidence intervals (95% CIs).

			Small cell carcinoma		Squamous cell carcinoma		Adenocarcinoma	
Follow-up (years)	Total (n)	Person-years	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)	Cases (n)	SIR (95% CI)
Antireflux surgery								
>1–34	34,752	425,008	31	0.58 (0.39–0.82)	59	0.70 (0.53–0.90)	101	0.88 (0.72–1.07)
>1–5	34,752	132,274	9	0.69 (0.32–1.31)	8	0.42 (0.18–0.83)	14	0.61 (0.34–1.03)
>5–10	31,066	138,898	4	0.24 (0.07–0.62)	22	0.88 (0.55–1.33)	29	0.87 (0.58–1.25)
>10–15	23,387	91,544	8	0.61 (0.26–1.20)	15	0.71 (0.40–1.17)	28	0.93 (0.62–1.35)
>15	12,986	62,292	10	0.92 (0.44–1.69)	14	0.72 (0.39–1.21)	30	1.06 (0.71–1.51)
No antireflux surgery								
>1–34	242,292	1,993,691	313	0.88 (0.78–0.98)	472	0.84 (0.77–0.92)	674	0.81 (0.75–0.87)
>1–5	242,292	808,109	121	0.92 (0.76–1.10)	190	0.91 (0.76–1.05)	239	0.83 (0.73–0.95)
>5–10	165,876	639,932	80	0.71 (0.56–0.88)	144	0.82 (0.69–0.97)	202	0.77 (0.67–0.88)
>10–15	93,809	329,116	63	0.98 (0.75–1.25)	79	0.79 (0.63–0.98)	137	0.86 (0.73–1.02)
>15	43,044	216,534	49	1.04 (0.77–1.37)	59	0.77 (0.59–1.00)	96	0.78 (0.63–0.95)

below 1 throughout the follow-up period. The HRs were not much influenced by adjustment for chronic obstructive pulmonary disease (Table 3A). The analyses of patients with objective GERD showed similar results as to the total GERD cohort, although most point estimates were slightly lower (Table 3B). The overall HRs were 0.55 (95% CI 0.36–0.84) for small cell carcinoma, 0.73 (95% CI 0.53–1.01) for squamous cell carcinoma and 0.95 (95% CI 0.74–1.21) for adenocarcinoma, and all point estimates were below 1 throughout the follow-up (Table 3B).

4. Discussion

This study indicates that patients who undergo antireflux surgery for GERD have decreased risks of small cell carcinoma and squamous cell carcinoma, but not of adenocarcinoma of the lung, compared with the background population as well as the non-operated patients with GERD.

Among methodological strengths of this study are the population-based design and the large cohort size, including most patients with a recorded diagnosis of GERD and those who had undergone antireflux surgery for GERD in any of the five Nordic countries. The long (up to 34 years) and complete follow-up are other advantages. The similar results from the analysis of the any GERD group and the objective GERD group indicate a low level of misclassification of GERD. The similar findings when comparing the antireflux surgery group with both the background population and non-operated patients with GERD also suggests validity of the results. A weakness is the risk of residual confounding despite adjustment for several confounders. The unavailability of direct data on tobacco smoking might be particularly relevant. Individuals selected for antireflux surgery might be less likely to be heavy tobacco smokers, and smoking is a risk factor for GERD and the three histological types of lung cancer under study [4,36]. However, a strong influence of confounding by smoking is less likely because of the weak association between

Table 3A
Risk of lung cancer by histological type among patients with any gastroesophageal reflux disease, comparing antireflux surgery with no such surgery and presented as hazard ratios (HRs) with 95% confidence intervals (CIs) from the Cox proportional hazard analyses.

Follow-up (years)	No antireflux surgery		Antireflux surgery			
	Cases (n)	HR (95% CI)	Cases (n)	Crude HR (95% CI)	Adjusted[a] HR (95% CI)	Adjusted[b] HR (95% CI)
Small cell carcinoma						
>1–34	724	1.00 (Reference)	43	0.51 (0.37–0.69)	0.64 (0.45–0.90)	0.63 (0.44–0.90)
>1–5	332	1.00 (Reference)	14	0.58 (0.34–0.99)	0.80 (0.43–1.48)	0.81 (0.44–1.49)
>5–10	200	1.00 (Reference)	7	0.30 (0.14–0.64)	0.38 (0.16–0.90)	0.37 (0.16–0.89)
>10–15	114	1.00 (Reference)	11	0.57 (0.31–1.06)	0.67 (0.32–1.40)	0.66 (0.32–1.37)
>15	78	1.00 (Reference)	11	0.62 (0.33–1.17)	0.72 (0.37–1.40)	0.71 (0.37–1.38)
Squamous cell carcinoma						
>1–34	1152	1.00 (Reference)	88	0.66 (0.53–0.82)	0.81 (0.63–1.04)	0.80 (0.62–1.03)
>1–5	550	1.00 (Reference)	16	0.40 (0.24–0.66)	0.58 (0.32–1.04)	0.58 (0.33–1.03)
>5–10	322	1.00 (Reference)	25	0.67 (0.44–1.00)	0.74 (0.45–1.22)	0.74 (0.45–1.21)
>10–15	160	1.00 (Reference)	19	0.71 (0.44–1.14)	0.87 (0.50–1.51)	0.86 (0.50–1.49)
>15	120	1.00 (Reference)	28	1.02 (0.68–1.54)	1.16 (0.74–1.81)	1.13 (0.72–1.77)
Adenocarcinoma						
>1–34	1774	1.00 (Reference)	142	0.70 (0.58–0.82)	1.04 (0.85–1.27)	1.03 (0.84–1.26)
>1–5	786	1.00 (Reference)	24	0.42 (0.28–0.62)	0.84 (0.53–1.33)	0.83 (0.52–1.32)
>5–10	562	1.00 (Reference)	42	0.64 (0.47–0.87)	1.08 (0.75–1.55)	1.07 (0.74–1.54)
>10–15	274	1.00 (Reference)	40	0.88 (0.63–1.22)	1.10 (0.74–1.63)	1.09 (0.73–1.62)
>15	152	1.00 (Reference)	36	1.05 (0.73–1.51)	1.13 (0.76–1.69)	1.12 (0.75–1.67)

[a] Adjusted for sex, age (continuous), calendar period, country, obesity diagnosis and diabetes mellitus type 2.
[b] Adjusted for sex, age (continuous), calendar period, country, obesity diagnosis, diabetes mellitus type 2 and chronic obstructive pulmonary disease.

smoking and GERD [4,37], and by the lack of influence of the adjustment for chronic obstructive pulmonary disease in the Cox regression analyses. Chronic obstructive pulmonary disease is namely strongly associated with smoking duration and intensity [38]. Confounding by other variables cannot be excluded, but except for smoking, the only established risk factors for GERD are obesity and heredity for GERD, which are not associated with the risk of lung cancer and should therefore not confound the results. Therefore, it was expected that adjustment for obesity diagnoses did not influence the HRs. The results from a study examining

Table 3B
Risk of lung cancer by histological type among patients with objective gastroesophageal reflux disease (reflux oesophagitis or Barrett's oesophagus), comparing antireflux surgery with no such surgery and presented as hazard ratios (HRs) with 95% confidence intervals (CIs) from the Cox proportional hazard analyses.

Follow-up (years)	No antireflux surgery		Antireflux surgery			
	Cases (n)	HR (95% CI)	Cases (n)	Crude HR (95% CI)	Adjusted[a] HR (95% CI)	Adjusted[b] HR (95% CI)
Small cell carcinoma						
>1–34	313	1.00 (Reference)	31	0.45 (0.31–0.65)	0.54 (0.35–0.83)	0.55 (0.36–0.84)
>1–5	121	1.00 (Reference)	9	0.46 (0.23–0.90)	0.51 (0.23–1.15)	0.52 (0.23–1.16)
>5–10	80	1.00 (Reference)	4	0.23 (0.08–0.63)	0.34 (0.11–1.09)	0.35 (0.11–1.09)
>10–15	63	1.00 (Reference)	8	0.45 (0.22–0.94)	0.54 (0.22–1.29)	0.54 (0.23–1.30)
>15	49	1.00 (Reference)	10	0.71 (0.36–1.40)	0.88 (0.43–1.82)	0.88 (0.43–1.81)
Squamous cell carcinoma						
>1–34	472	1.00 (Reference)	59	0.58 (0.44–0.76)	0.73 (0.53–1.01)	0.73 (0.53–1.01)
>1–5	190	1.00 (Reference)	8	0.26 (0.13–0.52)	0.42 (0.19–0.95)	0.43 (0.19–0.96)
>5–10	144	1.00 (Reference)	22	0.71 (0.45–1.11)	0.74 (0.42–1.31)	0.75 (0.43–1.32)
>10–15	79	1.00 (Reference)	15	0.69 (0.39–1.19)	0.91 (0.48–1.73)	0.91 (0.48–1.73)
>15	59	1.00 (Reference)	14	0.84 (0.47–1.51)	0.93 (0.49–1.76)	0.92 (0.48–1.74)
Adenocarcinoma						
>1–34	674	1.00 (Reference)	101	0.67 (0.55–0.83)	0.94 (0.74–1.21)	0.95 (0.74–1.21)
>1–5	239	1.00 (Reference)	14	0.36 (0.21–0.61)	0.75 (0.40–1.39)	0.74 (0.40–1.38)
>5–10	202	1.00 (Reference)	29	0.66 (0.45–0.98)	1.05 (0.66–1.66)	1.05 (0.66–1.66)
>10–15	137	1.00 (Reference)	28	0.73 (0.49–1.10)	0.85 (0.52–1.39)	0.86 (0.53–1.40)
>15	96	1.00 (Reference)	30	1.10 (0.73–1.66)	1.14 (0.72–1.82)	1.14 (0.72–1.82)

[a] Adjusted for sex, age (continuous), calendar period, country, obesity diagnosis and diabetes mellitus type 2.
[b] Adjusted for sex, age (continuous), calendar period, country, obesity diagnosis, diabetes mellitus type 2 and chronic obstructive pulmonary disease.

oesophageal adenocarcinoma from the same cohort showed no influence of antireflux surgery, further indicating that the antireflux surgery group was not selected compared with the background population or the non-operated group with GERD [39]. Another limitation is the potential influence of recurrence of GERD after antireflux surgery, which occurred in 17.7% of Swedish patients included in the cohort [40]. This exposure misclassification should not contribute to the overall associations, but rather dilute them. However, it could explain the lack of risk reductions over time after antireflux surgery. The lack of data on specific surgical codes prohibited separate analyses of specific types of antireflux surgery, but the commonly used antireflux surgery procedures have similar effects on GERD [41]. Histological misclassification of squamous cell carcinoma and adenocarcinoma of the lung is possible due to pathologic sub-typing disagreement. However, this has been shown to be limited and would only attenuate the reported risk estimates, not explain them [42,43]. The prevalence of GERD is comparable between Nordic countries and other Western countries [1,2], suggesting that the findings could be generalised to Western populations.

To our knowledge, no other study has investigated if antireflux surgery influences the risk of lung cancer. The decreased overall risks of small cell carcinoma and squamous cell carcinoma of the lung suggest a protective role of antireflux surgery. During follow-up, the risk reduction seemed more pronounced within 5–10 years for small cell carcinoma and 1–5 years for squamous cell carcinoma. A cancer preventive effect of antireflux surgery is expected to increase with longer follow-up; therefore, a cautious interpretation is necessary because of the lack of trend of further reduction in risk by time after surgery, although recurrence of GERD after surgery might be the explanation for this pattern [40]. More research is clearly needed to confirm these findings. Nevertheless, it is biologically plausible that antireflux surgery counteracts micro-aspiration of acidic and non-acidic duodenogastric content in patients with reflux, which may reduce inflammatory insults and subsequent oncogenic processes. This mechanism gains support by the finding that antireflux surgery in lung transplantation patients with GERD reduces pepsin levels in the lungs [44]. As described in detail elsewhere, antireflux medication was used by 92.1% of a sample of 199,466 non-operated GERD patients included in the present cohort [39]. The lower risk of lung cancer after antireflux surgery compared with antireflux medication use in the non-operated GERD groups is expected because antireflux medication does not prevent airway aspiration well. The findings of decreased risks of small cell carcinoma and squamous cell carcinoma, but not of adenocarcinoma, following antireflux surgery are well in line with the study hypotheses. This could be due to anatomical reasons, with small cell carcinoma and squamous cell carcinoma primarily arising in the central airways [29], anatomically closer to micro-aspirations than the peripheral airways, where adenocarcinoma mostly arise. These histology-specific differences should strengthen the reason for further studies of antireflux surgery and lung cancer.

Two cohort studies have found an increased risk of lung cancer in patients with GERD, which remained after controlling for tobacco smoking [17,18]. The slightly lower risk of lung cancer among non-operated GERD-patients compared with the background population in the present study was unexpected. Speculatively, the above-mentioned vast use of antireflux medication (mainly proton pump inhibitors) in non-operated GERD patients could possibly contribute to this finding. Although antireflux medication does not prevent airway micro-aspiration, it does reduce the acidity of the refluxate, which could theoretically decrease potential oncogenic inflammatory insults in the lungs. Individuals with GERD who seek in-hospital our outpatient specialised care might have greater health consciousness and thus may be more likely to take antireflux medication to alleviate their symptoms, less likely to smoke or more likely to stop smoking compared with the background population.

In conclusion, this large and population-based cohort study in the five Nordic countries suggests that GERD-patients who undergo antireflux surgery have a decreased risk of small cell carcinoma and squamous cell carcinoma, but not of adenocarcinoma of the lung.

Author involvement

Study concept and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: MY, GS, ENJ, JMO and JL. Drafting of the manuscript: MY. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: MY and GS. Obtained funding: JL. Study supervision: JL.

Funding

This work was supported by the Nordic Cancer Union (grant number 186058), Swedish Cancer Society (grant number 180684), and Swedish Research Council (grant number 340-2013-5478). Jesper Lagergren was supported by the United European Gastroenterology Research Prize and the Distinguished Professor Award at Karolinska Institutet.

Conflict of interest statement

Authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.07.018.

References

[1] Ness-Jensen E, Lindam A, Lagergren J, Hveem K. Changes in prevalence, incidence and spontaneous loss of gastro-oesophageal reflux symptoms: a prospective population-based cohort study, the HUNT study. Gut 2012;61(10):1390–7.

[2] El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014;63(6):871–80.

[3] Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus G. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101(8):1900–20. quiz 43.

[4] Ness-Jensen E, Lagergren J. Tobacco smoking, alcohol consumption and gastro-oesophageal reflux disease. Best Pract Res Clin Gastroenterol 2017;31(5):501–8.

[5] Pacheco A, Domingo C. Airway reflux: an emerging topic in respiratory medicine. Lancet Respir Med 2018;6(11):810–2.

[6] Broers C, Tack J, Pauwels A. Review article: gastro-oesophageal reflux disease in asthma and chronic obstructive pulmonary disease. Aliment Pharmacol Ther 2018;47(2):176–91.

[7] Ghisa M, Della Coletta M, Barbuscio I, Marabotto E, Barberio B, Frazzoni M, et al. Updates in the field of non-esophageal gastroesophageal reflux disorder. Expet Rev Gastroenterol Hepatol 2019;13(9):827–38.

[8] Hsu WT, Lai CC, Wang YH, Tseng PH, Wang K, Wang CY, et al. Risk of pneumonia in patients with gastroesophageal reflux disease: a population-based cohort study. PloS One 2017;12(8):e0183808.

[9] Hayes Jr D. A review of bronchiolitis obliterans syndrome and therapeutic strategies. J Cardiothorac Surg 2011;6:92.

[10] Houghton AM. Mechanistic links between COPD and lung cancer. Nat Rev Canc 2013;13(4):233–45.

[11] Langevin SM, Michaud DS, Marsit CJ, Nelson HH, Birnbaum AE, Eliot M, et al. Gastric reflux is an independent risk factor for laryngopharyngeal carcinoma. Cancer Epidemiol Biomark Prev 2013;22(6):1061–8.

[12] Parsel SM, Wu EL, Riley CA, McCoul ED. Gastroesophageal and laryngopharyngeal reflux associated with laryngeal malignancy: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019;17(7):1253–12564 e5.

[13] Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340(11):825–31.

[14] Lagergren J, Lagergren P. Recent developments in esophageal adenocarcinoma. CA - Cancer J Clin 2013;63(4):232–48.

[15] Agrawal K, Markert RJ, Agrawal S. Risk factors for adenocarcinoma and squamous cell carcinoma of the esophagus and lung. AME Med J 2018;3(3).

[16] Vereczkei A, Horvath OP, Varga G, Molnar TF. Gastroesophageal reflux disease and non-small cell lung cancer. Results of a pilot study. Dis Esophagus 2008;21(5):457–60.

[17] Choi WI, Jeong J, Lee CW. Association between EGFR mutation and ageing, history of pneumonia and gastroesophageal reflux disease among patients with advanced lung cancer. Eur J Canc 2019;122:101–8.

[18] Hsu CK, Lai CC, Wang K, Chen L. Risk of lung cancer in patients with gastro-esophageal reflux disease: a population-based cohort study. PeerJ 2016;4:e2753.

[19] Tutuian R, Vela MF, Hill EG, Mainie I, Agrawal A, Castell DO. Characteristics of symptomatic reflux episodes on Acid suppressive therapy. Am J Gastroenterol 2008;103(5):1090–6.

[20] Perrin-Fayolle M, Gormand F, Braillon G, Lombard-Platet R, Vignal J, Azzar D, et al. Long-term results of surgical treatment for gastroesophageal reflux in asthmatic patients. Chest 1989;96(1):40–5.

[21] Sontag SJ, O'Connell S, Khandelwal S, Greenlee H, Schnell T, Nemchausky B, et al. Asthmatics with gastroesophageal reflux: long term results of a randomized trial of medical and surgical antireflux therapies. Am J Gastroenterol 2003;98(5):987–99.

[22] Silva AP, Tercioti-Junior V, Lopes LR, Coelho-Neto Jde S, Bertanha L, Rodrigues PR, et al. Laparoscopic antireflux surgery in patients with extra esophageal symptoms related to asthma. Arq Bras Cir Dig 2014;27(2):92–5.

[23] Biswas Roy S, Elnahas S, Serrone R, Haworth C, Olson MT, Kang P, et al. Early fundoplication is associated with slower decline in lung function after lung transplantation in patients with gastroesophageal reflux disease. J Thorac Cardiovasc Surg 2018;155(6):2762–27671. e1.

[24] Hartwig MG, Anderson DJ, Onaitis MW, Reddy S, Snyder LD, Lin SS, et al. Fundoplication after lung transplantation prevents the allograft dysfunction associated with reflux. Ann Thorac Surg 2011;92(2):462–8. discussion; 8-9.

[25] Hoppo T, Jarido V, Pennathur A, Morrell M, Crespo M, Shigemura N, et al. Antireflux surgery preserves lung function in patients with gastroesophageal reflux disease and end-stage lung disease before and after lung transplantation. Arch Surg 2011;146(9):1041–7.

[26] Lortet-Tieulent J, Renteria E, Sharp L, Weiderpass E, Comber H, Baas P, et al. Convergence of decreasing male and increasing female incidence rates in major tobacco-related cancers in Europe in 1988-2010. Eur J Canc 2015;51(9):1144–63.

[27] Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Canc 2019;144(8):1941–53.

[28] de Sousa VML, Carvalho L. Heterogeneity in lung cancer. Pathobiology 2018;85(1–2):96–107.

[29] Giangreco A, Groot KR, Janes SM. Lung cancer and lung stem cells: strange bedfellows? Am J Respir Crit Care Med 2007;175(6):547–53.

[30] Maret-Ouda J, Wahlin K, Artama M, Brusselaers N, Farkkila M, Lynge E, et al. Cohort profile: the nordic antireflux surgery cohort (NordASCo). BMJ Open 2017;7(6):e016505.

[31] Maret-Ouda J, Tao W, Wahlin K, Lagergren J. Nordic registry-based cohort studies: possibilities and pitfalls when combining Nordic registry data. Scand J Publ Health 2017;45(17_suppl):14–9.

[32] Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449–90.

[33] Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Publ Health 2011;11:450.

[34] Sund R. Quality of the Finnish hospital discharge register: a systematic review. Scand J Publ Health 2012;40(6):505–15.

[35] Pukkala E, Engholm G, Hojsgaard Schmidt LK, Storm H, Khan S, Lambe M, et al. Nordic Cancer Registries - an overview of their procedures and data comparability. Acta Oncol 2018;57(4):440–55.

[36] Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med 2011;32(4):605–44.

[37] Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for,

gastro-oesophageal reflux symptoms: a meta-analysis. Gut 2018; 67(3):430–40.

[38] Bhatt SP, Kim YI, Harrington KF, Hokanson JE, Lutz SM, Cho MH, et al. Smoking duration alone provides stronger risk estimates of chronic obstructive pulmonary disease than pack-years. Thorax 2018;73(5):414–21.

[39] Maret-Ouda J, Santoni G, Wahlin K, Artama M, Brusselaers N, Farkkila M, et al. Esophageal adenocarcinoma after antireflux surgery in a cohort study from the 5 Nordic countries. Ann Surg 2019. https://doi.org/10.1097/SLA.0000000000003709.

[40] Maret-Ouda J, Wahlin K, El-Serag HB, Lagergren J. Association between laparoscopic antireflux surgery and recurrence of gastroesophageal reflux. JAMA 2017;318(10):939–46.

[41] Patti MG. An evidence-based approach to the treatment of gastroesophageal reflux disease. JAMA Surg 2016;151(1):73–8.

[42] da Cunha Santos G, Lai SW, Saieg MA, Geddie WR, Pintilie M, Tsao MS, et al. Cyto-histologic agreement in pathologic subtyping of non small cell lung carcinoma: review of 602 fine needle aspirates with follow-up surgical specimens over a nine year period and analysis of factors underlying failure to subtype. Lung Canc 2012;77(3):501–6.

[43] Zakowski MF, Rekhtman N, Auger M, Booth CN, Crothers B, Ghofrani M, et al. Morphologic accuracy in differentiating primary lung adenocarcinoma from squamous cell carcinoma in cytology specimens. Arch Pathol Lab Med 2016;140(10):1116–20.

[44] Fisichella PM, Davis CS, Lundberg PW, Lowery E, Burnham EL, Alex CG, et al. The protective role of laparoscopic antireflux surgery against aspiration of pepsin after lung transplantation. Surgery 2011;150(4):598–606.