Antireflux Surgery Versus Antireflux Medication and Risk of Esophageal Adenocarcinoma in Patients With Barrett's Esophagus

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e26. Learning Objective: Upon completion of this CME activity, successful learners will be able to explain Barrett's esophagus and compare treatment options for the condition.

See editorial on page 21.

BACKGROUND & AIMS: Antireflux treatment is recommended to reduce esophageal adenocarcinoma in patients with Barrett's esophagus. Antireflux surgery (fundoplication) counteracts gastroesophageal reflux of all types of carcinogenic gastric content and reduces esophageal acid exposure to a greater extent than antireflux medication (eg, proton pump inhibitors). We examined the hypothesis that antireflux surgery prevents esophageal adenocarcinoma to a larger degree than antireflux medication in patients with Barrett's esophagus. **METHODS:** This multinational and population-based cohort study included all patients with a diagnosis of Barrett's esophagus in any of the national patient registries in Denmark (2012–2020), Finland (1987–1996 and 2010–2020), Norway (2008–2020), or Sweden (2006–2020). Patients who underwent antireflux surgery were compared with nonoperated patients using antireflux medication. The risk of esophageal adenocarcinoma was calculated using multivariable Cox regression, providing hazard ratios (HRs) and 95% CIs adjusted for age, sex, country, calendar year, and comorbidity. **RESULTS:** The cohort consisted of 33,939 patients with Barrett's esophagus. Of these, 542 (1.6%) had undergone antireflux surgery. During up to 32 years of follow-up, the overall HR was not decreased in patients having undergone antireflux surgery compared with nonoperated patients using antireflux medication, but rather increased (adjusted HR, 1.9; 95% CI, 1.1–3.5). In addition, HRs did not decrease with longer follow-up, but instead increased for each follow-up category, from 1.8 (95% CI, 0.6–5.0) within 1–4 years of follow-up to 4.4 (95% CI, 1.4–13.5) after 10–32 years of follow-up. **CONCLUSIONS:** Patients with Barrett's esophagus who undergo antireflux surgery do not seem to have a lower risk of esophageal adenocarcinoma than those using antireflux medication.

Keywords: Fundoplication; Proton Pump Inhibitor; Esophageal Neoplasm; Multinational; Population-Based.

Esophageal adenocarcinoma is characterized by increasing incidence and poor prognosis, despite developments in treatment, highlighting the need for preventive measures.[1] Esophageal adenocarcinoma is usually preceded by Barrett's esophagus, a metaplasia of the epithelium in the distal esophagus caused by gastroesophageal reflux, which can progress from nondysplastic epithelium to low-grade dysplasia, high-grade dysplasia, and invasive esophageal adenocarcinoma.[2] Barrett's esophagus may be a target condition for esophageal adenocarcinoma preventive actions because it has a limited prevalence (1%–2% in population-based studies),[3,4] is readily identified at endoscopy, confirmed by means of histopathology, and carries a high absolute risk of esophageal adenocarcinoma.[2]

Antireflux treatment is recommended for patients with Barrett's esophagus to decrease the risk of esophageal adenocarcinoma. The dominating strategy is medication with a proton pump inhibitor, which reduces the acidity of the gastric content.[5,6] However, whether esophageal adenocarcinoma is indeed counteracted by such medication is uncertain, as meta-analyses have produced inconsistent results.[7,8] Antireflux surgery with fundoplication increases the ability of the gastroesophageal anatomic and physiological barrier to prevent reflux,[5] and can thus prevent any carcinogenic gastric content from reaching the esophagus, including both acid and bile.[9,10] In addition, randomized controlled trials have found that antireflux surgery reduces esophageal acid exposure to a greater extent than proton

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

It is uncertain whether antireflux surgery prevents esophageal adenocarcinoma to a larger degree than antireflux medication in patients with Barrett's esophagus. We conducted a population-based cohort study of all patients with known Barrett's esophagus (n = 33,939) in any of the Nordic countries of Denmark, Finland, Norway, or Sweden with up to 32 years of follow-up.

NEW FINDINGS

The risk of esophageal adenocarcinoma was not decreased in patients having undergone antireflux surgery compared with nonoperated patients using antireflux medication, but rather increased. The risk did not decrease with longer follow-up, but instead increased over time.

LIMITATIONS

Residual confounding cannot be excluded.

CLINICAL RESEARCH RELEVANCE

Antireflux surgery may not decrease the risk of esophageal adenocarcinoma more than antireflux medication among patients with Barrett's esophagus.

BASIC RESEARCH RELEVANCE

The mechanisms behind any preventive influence of antireflux treatment remain to be identified.

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pump inhibitor treatment.[11,12] Antireflux surgery may thus prevent esophageal adenocarcinoma better than antireflux medication. However, meta-analyses comparing antireflux surgery with antireflux medication for esophageal adenocarcinoma prevention in patients with Barrett's esophagus have been inconclusive. This could be explained by heterogeneity, selected and small samples, and short and incomplete follow-up among included studies.[13–15]

We aimed to examine the hypothesis that antireflux surgery prevents esophageal adenocarcinoma to a larger degree than antireflux medication in patients with Barrett's esophagus by conducting a large study of an unselected cohort with a long and complete follow-up.

Methods

Design

This was a population-based cohort study including all adults (18 years or older) with a recorded diagnosis of Barrett's esophagus in any of the patient registries in the Nordic countries of Denmark, Finland, Norway, and Sweden. The risk of esophageal adenocarcinoma was compared among patients who had undergone antireflux surgery and nonoperated patients using antireflux medication. Data came from a recently updated version of the Nordic Antireflux Surgery Cohort, which contains merged information from well-established nationwide health data registries in the Nordic countries. The original version of Nordic Antireflux Surgery Cohort has been described in detail elsewhere.[16] Personal identity codes, which are

mandatory for all residents of the Nordic countries and are used in all registries, enabled linkages of individuals' data among registries. Patients with Barrett's esophagus were identified from the patient registries (Supplementary Table 1). The total study period spanned from 1987 through 2020, but the start year varied among countries, depending on when specific diagnosis codes for Barrett's esophagus were introduced in the patient registries (2012 in Denmark, 1987 in Finland, 2008 in Norway, and 2006 in Sweden). In Finland, the diagnosis code for Barrett's esophagus was removed in 1996 and reintroduced in 2010, creating a gap in the inclusion of Finnish patients. Patients were excluded if they had an esophageal cancer diagnosis or had undergone esophagectomy (Supplementary Table 1) or antireflux surgery before Barrett's esophagus diagnosis. The study was approved by the relevant ethical committees, data inspectorates, and registry holders in the participating countries.[16]

Exposures

Antireflux surgery with fundoplication was compared with antireflux medication. Information regarding antireflux surgery was retrieved from the national patient registries, which have used the Nordic Medico-Statistical Committee Classification of Surgical Procedures[17] for coding of surgical procedures from 1997 onward, and country-specific procedural codes before 1997 (Supplementary Table 1). Information on whether the fundoplication was partial or total and anterior or posterior was not available in registries. Validation studies have found >97% concordance between data in the Swedish Patient Registry and operation charts for upper gastrointestinal surgical procedures.[18,19] Information on antireflux medication use was available for only a small part of all nonoperated participants in the present study. However, a large validation study conducted on Swedish patients included in the Nordic Antireflux Surgery Cohort showed that at least 97.3% of nonoperated patients with Barrett's esophagus dispensed a prescribed antireflux medication,[20] with a proton pump inhibitor as the drug of choice,[5] and clinical guidelines recommend life-long treatment.[6]

Outcome

The outcome was esophageal and gastroesophageal junctional adenocarcinoma (from here on "esophageal adenocarcinoma") originating from Barrett's esophagus. Gastroesophageal reflux–associated metaplastic origin of tumors was ensured by including only patients with histopathology-confirmed Barrett's esophagus. Esophageal adenocarcinoma was identified in the national cancer registries of the 4 participating countries (Supplementary Table 2). These registries are >96% complete overall,[16] and a comprehensive validation study found >98% completeness and 100% morphologic confirmation for esophageal adenocarcinoma in the Swedish Cancer Registry.[21] Censoring of follow-up due to mortality, including deaths abroad, was accomplished through linkage to the national death registries, which are 100% complete for date of death.[22]

Confounders

Five variables were considered potential confounders: age (continuous), sex (male or female), country (Denmark, Finland, Norway, or Sweden), calendar year (continuous), and comorbidity (Charlson Comorbidity Index score 0, 1, or ≥2).

Table 1. Characteristics of 33,939 Study Patients With Barrett's Esophagus

Characteristic	Antireflux medication	Antireflux surgery
Total, n (%)	33,397 (98.4)	542 (1.6)
Sex, n (%)		
Men	22,266 (66.7)	372 (68.6)
Women	11,131 (33.3)	170 (31.4)
Age at entry, y		
Mean (SD)	64.3 (13.3)	52.9 (12.6)
Median (IQR)	66 (56–74)	54 (44–80)
Charlson Comorbidity Index score, n (%)		
0	19,508 (58.4)	424 (78.2)
1	7940 (23.8)	91 (16.8)
≥2	5949 (17.8)	27 (5.0)
Calendar year		
Mean (SD)	2014 (4.6)	2005 (11.1)
Median (IQR)	2014 (2012–2017)	2010 (1994–2015)
Follow-up, y, mean (SD)	4.9 (3.7)	11.4 (9.3)
Country, n (%)		
Denmark	3421 (10.2)	51 (9.4)
Finland	5511 (16.5)	288 (53.1)
Norway	10,434 (31.2)	65 (12.0)
Sweden	14,031 (42.0)	138 (25.5)
Esophageal adenocarcinoma, n (%)	437 (1.3)	14 (2.6)
30-d mortality[a]	150 (0.5)	<4 (0.2)[b]

IQR, interquartile range.
[a]After Barrett's esophagus diagnosis or after antireflux surgery among patients with Barrett's esophagus.
[b]Due to privacy regulations in Denmark, numbers <4 were not allowed to be presented.

Comorbidities recorded within the last 5 years before inclusion into the cohort were used to calculate the Charlson Comorbidity Index score, using the most well-validated version (Supplementary Tables 3 and 4).[23,24] Data on all confounders were retrieved from the national patient registries. These registries record all diagnoses in inpatient hospital care and specialized outpatient care in the participating countries.[16] Positive predictive values of diagnoses in the patient registries ranged from 73%–88% in Denmark,[25] 75%–99% in Finland,[26] and 85%–95% in Sweden.[27] In Norway, only specific diagnoses have been validated,[28] with positive predictive values of >95%.[29]

Statistical Analysis

Patients who underwent antireflux surgery contributed exposed person-time from the date of surgery until the date of esophageal cancer, death, esophagectomy, or end of study period, whichever occurred first. Nonoperated patients (using antireflux medication) contributed unexposed person-time from the date of diagnosis of Barrett's esophagus until the date of esophageal cancer, death, esophagectomy, end of study period, or antireflux surgery, whichever occurred first. Patients initially included in the nonoperated group could thus cross over and contribute person-time to the antireflux surgery group from the date of surgery. The relative risk of developing esophageal adenocarcinoma during the follow-up was estimated using Cox regression, providing hazard ratios (HRs) and 95% CIs. A crude

model was unadjusted and a multivariable model was adjusted for the potential confounders and their categorizations presented above. The proportional hazard assumption was not met when computing the Schoenfeld residuals, hence we computed the HRs for 4 predefined follow-up categories: <1 year, 1–4 years, 5–9 years, 10–32 years after antireflux surgery, or diagnosis of Barrett's esophagus. Kaplan-Meier curves representing esophageal adenocarcinoma cancer-free survival were plotted. In a sensitivity analysis, patients having undergone endoscopic therapy for Barrett's esophagus (eg, endoscopic mucosal resection, endoscopic submucosal dissection, or radiofrequency ablation [Nordic Medico-Statistical Committee Classification of Surgical Procedures[17] codes JCA45 and JCA52]) were censored from the date of the procedure. The main analyses, however, included patients who had undergone endoscopic therapy for Barrett's esophagus. A senior biostatistician (G.S.) was responsible for the data management and statistical analyses. The analyses were performed using the statistical package Stata (version MP 15.01, StataCorp, College Station, TX) and followed a detailed study protocol, created and agreed upon by all authors before initiating the analyses.

Results

Patients

The cohort consisted of 33,939 patients with Barrett's esophagus. Of these, 542 patients (1.6%) had undergone

Table 2. Esophageal Adenocarcinoma in Patients With Barrett's Esophagus: Comparing Antireflux Surgery With Antireflux Medication

| | Antireflux medication | | | Antireflux surgery | | | |
Follow-up	Person-years	Cases, n	HR (95% CI)	Person-years	Cases, n	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
0–32 y	164,131	437	1.0 (reference)	6167	14	1.2 (0.7–2.0)	1.9 (1.1–3.5)
<1 y	31,410	152	1.0 (reference)	526	0	—	—
1–4 y	84,909	199	1.0 (reference)	1721	4	1.0 (0.4–2.7)	1.8 (0.6–5.0)
5–9 y	39,050	70	1.0 (reference)	1438	4	1.6 (0.6–4.4)	3.0 (1.0–8.6)
10–32 y	8761	16	1.0 (reference)	2482	6	2.6 (0.9–7.2)	4.4 (1.4–13.5)

[a]Adjusted for age, sex, country, calendar year, and comorbidity.

antireflux surgery. Characteristics of the operated and medicated study participants are presented in Table 1. The sex distribution was similar between the groups, but the antireflux surgery group was younger, had longer follow-up, and had fewer comorbidities compared with the antireflux medication group.

Risk of Esophageal Adenocarcinoma

Fourteen new cases of esophageal adenocarcinoma occurred during follow-up of the antireflux surgery group and 437 in the antireflux medication group. The overall HR of esophageal adenocarcinoma was increased in the surgery group compared with the medication group (adjusted HR, 1.9; 95% CI, 1.1–3.5). This association remained after excluding the first year of follow-up (adjusted HR, 2.7; 95% CI, 1.4–5.0). The HRs did not decrease over time after antireflux surgery, but instead tended to increase for each follow-up period,

from 1.8 (95% CI, 0.6–5.0) within 1–4 years of follow-up to 4.4 (95% CI, 1.4–13.5) after 10–32 years of follow-up (Table 2). A similar pattern was found in Kaplan-Meier analyses of esophageal adenocarcinoma cancer-free survival (Figure 1). After censoring of patients who underwent endoscopic therapy of Barrett's esophagus, the results were consistent with those of the main analysis, showing an overall adjusted HR of 2.2 (95% CI, 1.2–3.9) in the antireflux surgery group and increasing HRs for each longer follow-up period (Table 3).

Discussion

In this cohort of patients with Barrett's esophagus, the risk of esophageal adenocarcinoma did not decrease after antireflux surgery compared with antireflux medication. Instead, the risk was increased throughout the follow-up among patients having undergone antireflux surgery.
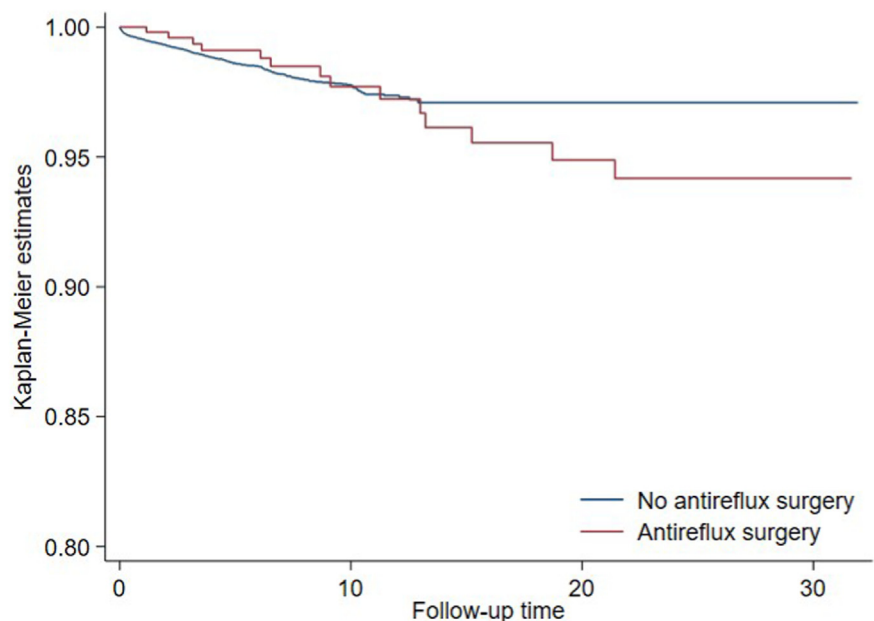

Figure 1. Kaplan-Meier curves comparing esophageal adenocarcinoma cancer-free survival after antireflux surgery and antireflux medication.

Table 3. Esophageal Adenocarcinoma in Patients With Barrett's Esophagus: Comparing Antireflux Surgery With Antireflux Medication After Censoring of Patients Who Underwent Endoscopic Therapy for Barrett's Esophagus

| | Antireflux medication | | | Antireflux surgery | | | |
Follow-up	Person-years	Cases, n	HR (95% CI)	Person-years	Cases, n	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
0–32 y	162,162	410	1.0 (Reference)	6098	14	1.3 (0.7–2.2)	2.2 (1.2–3.9)
<1 y	31,203	145	1.0 (Reference)	518	0	—	—
1–4 y	83,927	186	1.0 (Reference)	1692	4	1.1 (0.4–2.9)	2.0 (0.7–5.7)
5–9 y	38,408	66	1.0 (Reference)	1417	4	1.7 (0.6–4.7)	3.3 (1.1–9.7)
10–32 y	8623	13	1.0 (Reference)	2471	6	3.2 (1.1–9.3)	5.8 (1.8–18.7)

[a]Adjusted for age, sex, country, calendar year, and comorbidity.

Among the strengths of this study is the multinational and population-based design, resulting in a large and unselected cohort of patients with histopathology-confirmed Barrett's esophagus. The follow-up was long (up to 32 years) and complete. Data on key variables, that is, Barrett's esophagus, antireflux surgery, esophageal adenocarcinoma, and confounders, were obtained from well-validated and nationwide health data registries.[18,19,21,25–27,29] and the results were adjusted for several potential confounders. Thus, the results should be internally valid and generalizable to countries with health care similar to that in the Nordic countries. A limitation is the possibility of confounding factors that were not available and could possibly influence the choice between surgery and medication, for example, tobacco smoking, body mass index, and length of Barrett's segment. However, diagnoses associated with smoking and obesity were captured in the Charlson Comorbidity Index and, therefore, to some extent adjusted for, and it is unlikely that the choice of conducting antireflux surgery or not was influenced by the Barrett's segment length. It might be argued that the surgical group could represent a more severe disease state than the medication group. However, all patients (operated and nonoperated) had confirmed Barrett's esophagus, and there is no reason to believe that levels of dysplasia differed between groups. Nevertheless, high-grade dysplasia had been treated throughout the study period, and endoscopic treatment of low-grade dysplasia has become increasingly common.[6,30] The sensitivity analysis excluding patients who underwent endoscopic treatment did not show any difference in results compared with the main analyses, which is further reassuring. The length of metaplasia required for a Barrett's esophagus diagnosis decreased during the study period,[30] but this should not influence the results because HRs were adjusted for calendar year. Data on medication use were not available for most of the nonoperated patients in the present study cohort, but any underuse of antireflux medication should have been low and would not have contributed to the increased risk found in the antireflux surgery group. Another limitation was the limited size of the antireflux surgery group and the low number of patients developing esophageal adenocarcinoma after such surgery, which reduced the statistical power, particularly in subgroup analyses.

Three meta-analyses have attempted to compare antireflux surgery and antireflux medication for esophageal adenocarcinoma prevention among patients with Barrett's esophagus. Two of these did not find any significant differences in risk,[13,14] and the third found a reduced risk after antireflux surgery when restricted to the 4 studies published after the year 2000, although the main analysis using all included studies found no such association.[15] Most of the studies included in these meta-analyses came from single centers, were of small sample size, examined only 1 treatment arm, and had a short or incomplete follow-up, and all 3 meta-analyses were hampered by heterogeneity among the included studies. In alignment with the findings of the present study, 3 population-based cohort studies among patients with gastroesophageal reflux disease (GERD), although not specifically examining Barrett's esophagus, instead found an increased risk of esophageal adenocarcinoma after antireflux surgery compared with nonoperated patients.[20,31,32]

Antireflux surgery is often reserved for patients with severe GERD and is conducted only after long periods of persisting symptoms despite the use of antireflux medications. The strict selection is illustrated by the low proportion of patients who underwent antireflux surgery in the present cohort. Barrett's esophagus is caused by chronic or repeated tissue injury from GERD, but not all patients with Barrett's esophagus have severe reflux symptoms.[3] Because the risk of esophageal adenocarcinoma increases with reflux symptom duration and severity,[33] it is not surprising that patients selected for antireflux surgery in the present cohort had a higher baseline risk of esophageal adenocarcinoma than those in the antireflux medication group. If antireflux surgery would have a substantially greater cancer-preventative effect in Barrett's esophagus patients compared with antireflux medication, we would expect decreasing risk estimates over time after surgery, which was not found in this study.

Recurrence of GERD symptoms occurs in approximately 15% of patients who have undergone antireflux surgery and might contribute to the lack of superiority over antireflux medication for esophageal adenocarcinoma prevention.[34,35] However, the intention-to-treat approach was used, that is, patients who used antireflux medication after surgery remained in the analyses. Although it seems logical that antireflux surgery would have a better cancer-preventive effect than antireflux medication due to the greater reduction in esophageal acid exposure and the ability to prevent all types of carcinogenic gastric content from reaching the esophagus, performing antireflux surgery after years of GERD may be too late to enable a cancer-preventative effect, and most of the patients first diagnosed with Barrett's esophagus reported a history of many years of GERD symptoms.[36,37] Such long duration of GERD symptoms has been associated with a substantial increase in the risk of esophageal adenocarcinoma[33,38] and suggests the carcinogenesis has progressed too far to be halted in this cohort of patients with Barrett's esophagus. Nevertheless, with current clinical practice of antireflux surgery, often performed after long periods of persisting GERD, both in patients with Barrett's esophagus and in those without,[39,40] there remains little room to motivate antireflux surgery for cancer-preventative reasons alone. Patients who have undergone antireflux surgery seem to remain at an elevated risk of developing esophageal adenocarcinoma.

In conclusion, this multinational and population-based cohort study of patients with Barrett's esophagus with a long and complete follow-up indicated that patients who undergo antireflux surgery do not have a lower risk of esophageal adenocarcinoma than those using antireflux medication. Instead, patients with Barrett's esophagus who undergo antireflux surgery remain at an increased risk of esophageal adenocarcinoma and should continue taking part in surveillance programs.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2023.08.050.

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GI CANCER

Supplementary Table 1. International Classification of Diseases Diagnosis Codes for Barrett's Esophagus and Nordic Medico-Statistical Committee Classification of Surgical Procedures Codes for Esophagectomy and Antireflux Surgery

Variable	Denmark	Finland	Norway	Sweden
Barrett's esophagus	ICD-10: DK22.7	ICD-9: 5301B ICD-10: K22.7	ICD-10: K22.7	ICD-10: K22.7
Esophagectomy	Country-specific codes: 41060, 41080 NOMESCO: JCC	Country-specific codes: 6201-6205, 6209 NOMESCO: JCC	NOMESCO: JCC	Country-specific codes: 2820-2822, 2829 NOMESCO: JCC
Antireflux surgery	Country-specific code: 41795 NOMESCO: JBC	Country-specific codes: 6241, 6242 NOMESCO: JBC	NOMESCO: JBC	Country-specific code: 4272 NOMESCO: JBC

ICD-9, International Classification of Diseases, 9th Revision[e1]; ICD-10, International Classification of Diseases, 10th Revision[e2]; NOMESCO, Nordic Medico-Statistical Committee Classification of Surgical Procedures.[17]

Supplementary Table 2. International Classification of Diseases Codes and Histopathology Codes for Esophageal Cancer

Variable	Codes defining esophageal and cardia cancer
Anatomic localization	
ICD-7	150 (all with correct first 3 positions), 151.1
ICD-10/-O2/-O3	C15 (all with correct first 3 positions), C16.0
Histology	
Esophageal and cardia adenocarcinoma	
Swedish pathology code	096
ICD-10/ICD-O-2/ICD-O-3[a]	8140–8149, 8160–8162, 8190–8221, 8260–8337, 8350–8551, 8570–8576, 8940–8941
Esophageal squamous cell carcinoma	
ICD-10/ICD-O-2/ICD-O-3[a]	8051–8084, 8120–8131
PAD	146

ICD-7, International Classification of Diseases, 7th Revision[e3]; ICD-10, International Classification of Diseases, 10th Revision[e2]; ICD-O-2, International Classification of Diseases for Oncology, Second Edition[e4]; ICD-O-3, International Classification of Diseases for Oncology, Third Edition.[e5]
[a]Fifth digit = 3 or behavior variable = 3 (for Denmark fifth digit = 3 or 9) means malignant tumor.

Supplementary Table 3. International Classification of Diseases Codes Included in the Charlson Comorbidity Index

Variable	ICD-8 Denmark (1977–1993) Finland (1969–1986) Norway (no use) Sweden (1964–1986)	ICD-9 Denmark (No use) Finland (1987–1995) Norway (no use) Sweden (1987–1996)	ICD-10 Denmark (1993) Finland (1996) Norway (1997) Sweden (1997)
Myocardial infarction	410[a], 412[a]	410[a], 412[a]	I21[a]–I23[a], I252[a]
Congestive heart failure	427[a], 428[a]	402[a], 425[a], 428[a], 429D[a b]	I11[a], I13[a], I255[a], I42[a]-I43[a], I50[a], I517[a]
Peripheral vascular disease	440[a]–445[a]	440[a]–447[a], V43E[a b], 785E[a b]	I70[a]–I73[a], I770[a]–I771[a], K551[a], K558[a]–K559[a], R02[a], Z958[a]–Z959[a]
Cerebrovascular disease	430[a]–438[a]	430[a]–438[a], 362D[a b]	G45[a]–G46[a], I60[a]–I69[a]
Dementia	290[a]	290[a], 294B[a b]	A810[a], F00[a]–F03[a], F051[a], G30[a]–G31[a]
Chronic pulmonary disease	490[a]–493[a], 515[a]–518[a]	490[a]–496[a], 500[a]–505[a], 416[a], 506E[a b]	I26[a]–I27[a], J40[a]–J47[a], J60[a]–J67[a], J684[a], J701[a], J703[a]
Rheumatic disease	710[a]–712[a], 734[a]	710[a]–714[a], 725[a]	M05[a]–M06[a], M09[a], M120[a], M315[a], M32[a]–M36[a]
Liver disease	070[a], 4560[a], 571[a], 573[a]	070[a], 571[a]–573[a] 456A[a b]-456C[a b]	B18[a], I85[a], I864[a], I982[a], K70[a]–K71[a], K721[a], K729[a], K76[a], R162[a], Z944[a]
Diabetes mellitus	250[a]	250[a]	E10[a]-E14[a]
Hemiplegia	344[a]	342[a]-344[a]	G114[a], G81[a]-G83[a]
Renal disease	403[a]–404[a], 580[a]–583[a], 792[a]	403[a]–404[a], 580–588[a], V42A[a b], V45B[a b]	I12[a]–I13[a], N01[a], N03[a], N05[a], N07[a]–N08[a], N171[a]–N172[a], N18[a], N19[a], N25[a], Z49[a], Z940[a], Z992[a]
Any malignancy	140[a]–172[a], 174[a]–195[a], 200[a]–207[a]	140[a]–172[a], 174[a]–195[a], 200[a]–208[a]	C00[a]–C26[a], C30[a]–C34[a], C37[a]–C41[a], C43[a], C45[a]-C58[a], C60–C76[a], C80[a]-C85[a], C88[a], C90[a]–C97[a]
Metastatic tumors	196[a]–199[a]	196[a]–199[a]	C77[a]–C79[a]
AIDS		279K[a b]	B20[a]–B24[a]

ICD-8, International Classification of Diseases, 8th Revision[e6]; ICD-9, International Classification of Diseases, 9th Revision[e1]; ICD-10, International Classification of Diseases, 10th Revision.[e2]

[a]All positions that follow are valid without need for further specification.

[b]The corresponding code in Finland is different (see Supplementary Table 4).

Supplementary Table 4. International Classification of Diseases, 9th Revision Codes in Supplementary Table 3 That Correspond to a Different Code in Finland

Variable	ICD-9 Finland
Myocardial infarction	—
Congestive heart failure	429D[a]→4293A[a]
Peripheral vascular disease	V43E[a]→No corresponding code 785E[a]→7854A[a]
Cerebrovascular disease	362D[a]→3623A[a]-3623D[a]
Dementia	294B[a]→2941A[a]
Chronic pulmonary disease	506E→5064A[a]
Rheumatic disease	—
Liver disease	456A[a]–456C[a]→4560A[a], 4561A[a]
Diabetes mellitus	—
Hemiplegia	—
Renal disease	V42A[a]→No corresponding code V45B[a]→No corresponding code
Any malignancy	—
Metastatic tumors	—
AIDS	279K[a]→0788C[a]

ICD-9, International Classification of Diseases, 9th Revision.[e1]
[a]All positions that follow are valid without need for further specification.

Supplementary References

e1. International Classification of Diseases, 9th Revision. World Health Organization, 1976.

e2. International Classification of Diseases, 10th Revision. World Health Organization, 1990.

e3. International Classification of Diseases, 7th Revision. World Health Organization, 1956.

e4. International Classification of Diseases for Oncology. Second Edition. World Health Organization, 1990.

e5. International Classification of Diseases for Oncology. Third Edition. World Health Organization, 2013.

e6. International Classification of Diseases, 8th Revision. World Health Organization, 1966.