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Incidence and Mortality in Upper Gastrointestinal Cancer After Negative Endoscopy for Gastroesophageal Reflux Disease

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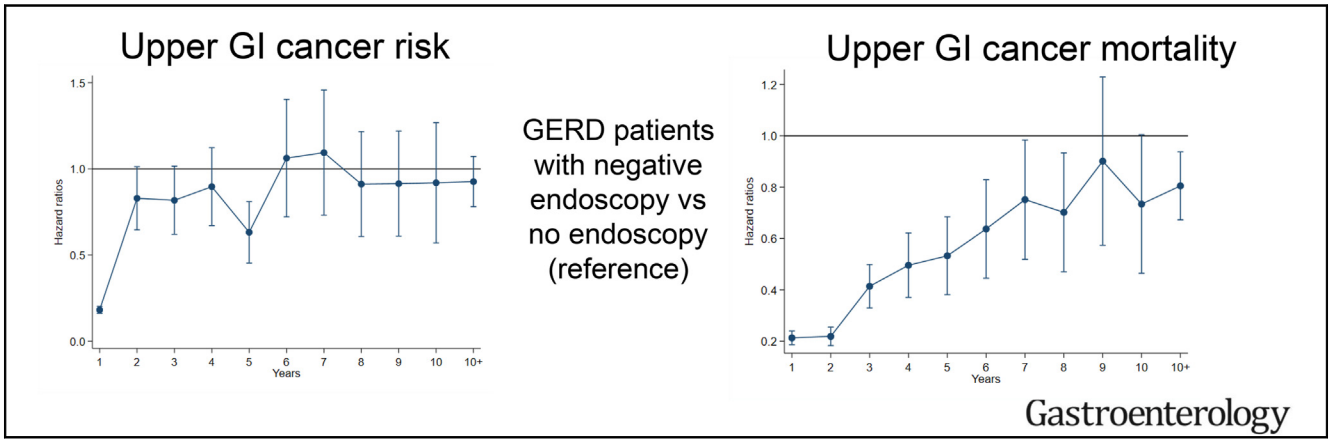
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e20. Learning Objective: Upon completion of this CME activity, successful learners will be able to discuss the prevalence of gastroesophageal reflux disease, indications for upper endoscopy in patients with gastroesophageal reflux disease, and risk of esophageal adenocarcinoma in patients with Barrett's esophagus.



See Covering the Cover synopsis on page 357.

BACKGROUND AND AIMS: Gastroesophageal reflux disease (GERD) is associated with an increased risk of cancer of the upper gastrointestinal tract. This study aimed to assess whether and to what extent a negative upper endoscopy in patients with GERD is associated with decreased incidence and mortality in upper gastrointestinal cancer (ie, esophageal, gastric, or duodenal cancer). **METHODS:** We conducted a population-based cohort study of all patients with newly diagnosed GERD between July 1, 1979 and December 31, 2018 in Denmark, Finland, Norway, and Sweden. The exposure, negative upper endoscopy, was examined as a time-varying exposure, where participants contributed unexposed person-time from GERD diagnosis until screened and exposed person-time from the negative upper endoscopy. The incidence and mortality in upper gastrointestinal cancer were assessed using parametric flexible models, providing adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). **RESULTS:** Among 1,062,740 patients with GERD (median age 58 years; 52% were women) followed for a mean of 7.0 person-years, 5324 (0.5%) developed upper gastrointestinal cancer and 4465 (0.4%) died from such cancer. Patients who had a negative upper endoscopy had a 55% decreased risk of upper gastrointestinal cancer compared with those who did not undergo endoscopy (HR, 0.45; 95% CI, 0.43–0.48), a decrease that was more pronounced during more recent years (HR, 0.34; 95% CI, 0.30–0.38 from 2008 onward), and was otherwise stable across sex and age groups. The corresponding reduction in upper gastrointestinal mortality among patients with upper endoscopy was 61% (adjusted HR, 0.39; 95% CI, 0.37–0.42). The risk reduction after a negative upper endoscopy in incidence and mortality lasted for 5 and at least 10 years, respectively. **CONCLUSIONS:** Negative upper endoscopy is associated with strong and long-lasting decreases in incidence and mortality in upper gastrointestinal cancer in patients with GERD.

Keywords: Gastroesophageal Reflux Disease; Esophageal Neoplasm; Gastric Neoplasm; Gastroscopy.

Abbreviations used in this paper: **CI, confidence interval; GERD, gastroesophageal reflux disease; HR, hazard ratio.**

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Gastroesophageal reflux disease (GERD) is characterized mainly by troublesome and recurrent symptoms of heartburn or acid regurgitation, and 20%–30% of the general population in Western countries report at least weekly symptoms of GERD.[1,2] GERD is the most common indication for referral for upper endoscopy (esophagogastroduodenoscopy) to evaluate complications and underlying diseases.[3,4] However, upper endoscopy frequently returns completely negative results and is not required for determining GERD diagnosis.[5,6] Instead, typical symptoms of GERD that respond to a short-term trial treatment with a proton pump inhibitor may suffice for diagnosis.[7,8] Although GERD is a benign disease, it is causally linked with the premalignant condition, Barrett's esophagus, and esophageal and gastric cardia adenocarcinoma, which are usually readily detected by upper endoscopy for GERD.[9,10] Upper endoscopy is also the reference standard for determining the diagnosis of other histologic types of esophageal cancer, gastric noncardia cancer, and duodenal cancer, which can also present with symptoms of GERD or dyspepsia, as well as premalignant lesions of these tumors. It is unclear whether upper endoscopy in patients with GERD is associated with a risk reduction in the development of upper gastrointestinal cancer (ie, esophageal, gastric, or duodenal cancer) or death from these tumors. The aim of this study was to assess whether and to what extent a negative upper endoscopy for GERD decreases incidence and mortality in upper gastrointestinal cancer, and also to estimate how long any such risk reductions may last.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

GERD is associated with upper gastrointestinal cancer and is a frequent indication for upper endoscopy, but whether endoscopy is associated with a decreased cancer incidence and mortality is uncertain.

NEW FINDINGS

In a population-based 4-nation cohort study of 1,062,740 patients with GERD, a normal upper endoscopy was followed by 55% decreased cancer incidence and 61% decreased cancer-related mortality.

LIMITATIONS

There are no direct data on some potential confounders, for example, smoking, body mass index, alcohol consumption, and lifestyle habits.

IMPACT

Upper endoscopy was followed by a strongly decreased cancer incidence and mortality for 5–10 years, indicating that a 1-time upper endoscopy for patients with GERD is beneficial.

Methods

Design

This was a population-based cohort study encompassing all health care in the 4 Nordic countries of Denmark, Finland, Norway, and Sweden during the study period between July 1, 1979 and December 31, 2018. The study was based on an updated version of a Nordic cohort of patients with GERD (NordASCo), which consists of data retrieved from national patient registries, cancer registries, and cause of death registries in all 4 countries.[11] The GERD diagnosis was identified from the relevant diagnosis codes in national patient registries (Supplementary Table 1). The study was restricted to patients with GERD because they have a relatively high risk of upper gastroesophageal cancer and comprise a large proportion of endoscopies performed. Exclusion criteria were age younger than 18 years or 90 years and older, previous diagnosis of upper gastrointestinal cancer, upper endoscopy, or endoscopic or surgical treatment of the upper gastrointestinal tract before enrollment (Figure 1 and Supplementary Tables 2–3). Approvals were obtained from all relevant ethical review boards and data inspectorates in the participating countries.[11]

Exposure

The exposure was a negative upper endoscopy, defined as a lack of a diagnosis of upper gastrointestinal cancer within 6 months of the endoscopy. The endoscopy was identified from the national patient registries using the relevant procedural codes (Supplementary Table 4). In a sensitivity analysis, the definition of negative endoscopy was broadened to exclude all premalignant conditions of the upper gastrointestinal tract in addition to invasive cancer (Supplementary Table 5).

Outcomes

The main outcome was a new diagnosis of any upper gastrointestinal cancer, that is, gastric, esophageal, or duodenal cancer. The following were secondary outcomes: mortality due to upper gastrointestinal cancer, incidence of esophageal adenocarcinoma specifically, and mortality from esophageal adenocarcinoma specifically. The codes determining the incidence and mortality of the studied tumors were identified from the national cancer registries and cause of death registries, respectively (Supplementary Table 6).

Confounders

The following 5 variables were considered potential confounding factors: age, sex, comorbidity, calendar year, and country. Information about these variables was collected from

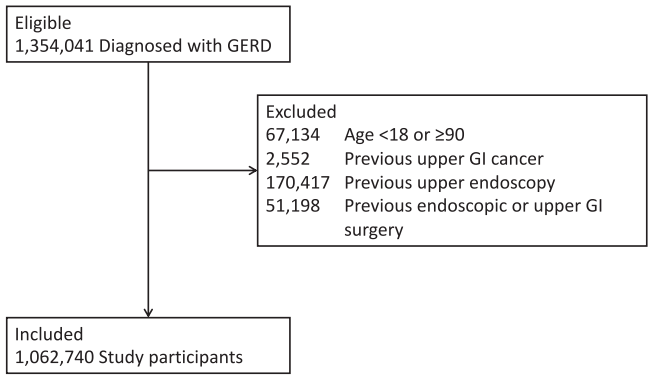

Figure 1. Selection of the study participants eligible for upper endoscopy.

the patient registries. Comorbidity was classified according to the most up-to-date and well-validated version of the Charlson Comorbidity Index.[12]

Statistical Analysis

The exposure (negative upper endoscopy) was used as a time-varying variable. Patients without endoscopy contributed unexposed person-time from the date of GERD diagnosis until a negative upper endoscopy was obtained, upper gastrointestinal cancer diagnosis, death, or the end of the study period, whichever occurred first. Patients diagnosed with cancer within 6 months of a first endoscopy were classified as unexposed cases. Whenever an endoscopy was negative, the exposure status changed from unexposed to exposed and the variables age and comorbidity were updated. Participants then contributed to exposed person-time until another negative upper endoscopy was obtained, upper gastrointestinal cancer diagnosis, death, or the end of the study period. Control endoscopies within 6 months of the index endoscopy were not considered censoring events and all tumors diagnosed within these 6 months were classified as exposed cases.

Parametric flexible models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for the outcomes, and compared different lengths of follow-up after a negative upper endoscopy.[13] The HRs were adjusted for the 5 confounders with the following categorizations: sex (female or male), age (continuous), comorbidity (Charlson Comorbidity Index 0, 1, or $\geq$2), calendar year (dichotomized by the median year into 2008 or before and after 2008), and country (Denmark, Finland, Norway, or Sweden). Analyses were also stratified by sex (female and male), age (younger than 50 years and 50 years or older), and calendar year (2008 or before and after 2008). The HRs and 95% CIs for the outcomes were graphed over years of follow-up across exposed and nonexposed person-time to examine the durability of any risk reduction after a negative endoscopy. The proportionality of the hazard was not met in the analysis, but we reported the overall HR over time. Likelihood ratio tests were applied to assess heterogeneity in the subgroup analyses. All data management and statistical analyses were performed by an experienced biostatistician (G.S.) who followed a detailed, planned study protocol and used STATA software (version 16, Stata Corp).

Results

Participants

The study included 1,062,740 patients with newly diagnosed GERD. Patient characteristics are presented in Table 1. The median age was 58 years and 52% were women. During 3,036,104 unexposed person-years of follow-up, that is, the time period during which no endoscopies were performed, 3601 patients (0.34%) developed upper gastrointestinal cancer and 2856 (0.27%) died due to upper gastrointestinal cancer. Among 736,759 patients (69.3%) with a negative upper endoscopy, who contributed 4,429,751 exposed person-years, 1723 (0.23%) developed upper gastrointestinal cancer and 1609 (0.22%) died due to upper gastrointestinal cancer.

Table 1. Characteristics of 1,062,740 Participants With Newly Diagnosed Gastroesophageal Reflux Disease in Any of 4 Nordic Countries

Characteristic	Total cohort	Negative upper endoscopy
Participants, n (%)	1,062,740 (100.0)	736,759 (100.0)
Mean follow-up, *y*	7.0	6.1
Age, *y*, median (interquartile range)	58.0 (44.5–70.0)	58.0 (45.0–70.0)
Aged younger than 50 y, n (%)	353,085 (33.2)	245,268 (33.3)
Aged 50 years or older, n (%)	709,655 (66.8)	491,491 (66.7)
Sex, n (%)		
Male	511,099 (48.1)	357,216 (48.5)
Female	551,641 (51.9)	379,543 (51.5)
Calendar year, n (%)		
2008 or before	555,516 (52.3)	363,153 (49.3)
After 2008	507,224 (47.7)	373,606 (50.7)
Charlson Comorbidity Index, n (%)		
0	798,703 (75.2)	570,054 (77.4)
1	181,740 (17.1)	117,554 (15.9)
$\geq$2	82,297 (7.7)	49,151 (6.7)
Country, n (%)		
Denmark	182,893 (17.2)	149,656 (20.3)
Finland	221,538 (20.9)	128,066 (17.4)
Norway	182,008 (17.1)	128,789 (17.5)
Sweden	476,301 (44.8)	330,248 (44.8)

Incidence of Upper Gastrointestinal Cancer

The incidence rate of upper gastrointestinal cancer during unexposed person-time in patients with GERD was 119 (95% CI, 115–123) per 100,000 person-years. The corresponding rate after a negative upper endoscopy was 38 (95% CI, 37–40) per 100,000 person-years. The risk of upper gastrointestinal cancer was 55% decreased in participants with a negative upper endoscopy compared with those without endoscopy (adjusted HR, 0.45; 95% CI, 0.43–0.48) (Table 2). The risk reduction was similar in separate analyses of esophageal cancer (adjusted HR, 0.48; 95% CI, 0.44–0.51) and gastric cancer (adjusted HR, 0.41; 95% CI, 0.38–0.45), and remained across sexes, age groups, and calendar periods. The magnitude of the risk reduction was also similar across sexes and age groups, but was more pronounced in the more recent calendar period (adjusted HR, 0.34; 95% CI, 0.30–0.38; $P < .001$) (Table 2). The decreased risk of upper gastrointestinal cancer after a negative upper endoscopy was most pronounced during the first year of follow-up, but risk reduction lasted for 5 years (Figure 2). In the sensitivity analysis redefining negative

Table 2. Risk of Upper Gastrointestinal Cancer After a Negative Upper Endoscopy, Overall and Stratified by Sex, Age, and Calendar Year

Variable	Person-years, n	Cases, n	Incidence rate[a]	Unadjusted HR (95% CI)	Adjusted[b] HR (95% CI)
Overall					
Negative upper endoscopy					
No	3,036,104	3601	118.6	1.00 (Reference)	1.00 (Reference)
Yes	4,475,929	1723	38.5	0.44 (0.41–0.46)	0.45 (0.43–0.48)
Men					
Negative upper endoscopy					
No	1,441,202	2393	166.0	1.00 (Reference)	1.00 (Reference)
Yes	2,182,135	1151	52.7	0.43 (0.40–0.46)	0.44 (0.41–0.48)
Women					
Negative upper endoscopy					
No	1,594,902	1208	75.7	1.00 (Reference)	1.00 (Reference)
Yes	2,293,794	572	24.9	0.44 (0.40–0.49)	0.46 (0.42–0.51)
Aged younger than 50 y					
Negative upper endoscopy					
No	1,155,509	305	26.4	1.00 (Reference)	1.00 (Reference)
Yes	1,754,459	204	11.6	0.58 (0.48–0.69)	0.57 (0.48–0.69)
Aged 50 y or older					
Negative upper endoscopy					
No	1,880,596	3296	175.3	1.00 (Reference)	1.00 (Reference)
Yes	2,721,469	1519	55.8	0.43 (0.40–0.46)	0.43 (0.41–0.46)
2008 or before					
Negative upper endoscopy					
No	2,319,849	2403	103.6	1.00 (Reference)	1.00 (Reference)
Yes	3,247,092	1268	39.1	0.48 (0.45–0.51)	0.51 (0.48–0.55)
After 2008					
Negative upper endoscopy					
No	716,256	1198	167.3	1.00 (Reference)	1.00 (Reference)
Yes	1,228,837	455	37.0	0.35 (0.32–0.39)	0.34 (0.30–0.38)

[a]Per 100,000 person-years.
[b]Adjusted for sex, age, calendar year, Charlson Comorbidity Index, and country (unless the variable was used for stratification).

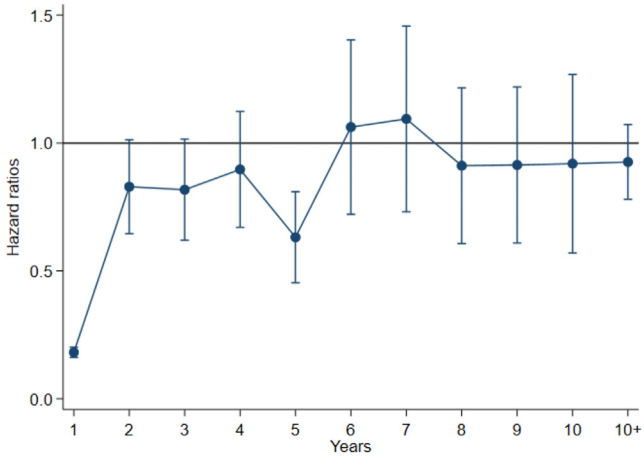

Figure 2. Adjusted risk of upper gastrointestinal cancer by year of follow-up after a negative upper endoscopy in patients with GERD.

endoscopy as without any upper gastrointestinal cancer or premalignant lesion, 974,788 patients were included, of which 655,668 had a negative endoscopy. In this analysis, the risk reduction of upper gastrointestinal cancer after a negative upper endoscopy was similarly decreased (adjusted HR, 0.46; 95% CI, 0.43–0.49) (Table 3).

Mortality Due to Upper Gastrointestinal Cancer

Among GERD patients without a negative upper endoscopy, the mortality in upper gastrointestinal cancer was 94 (95% CI, 90–97) per 100,000 person-years, and the median survival from cancer diagnosis was 0.7 years (interquartile range, 0.2–1.7 years). In patients with a negative upper endoscopy, mortality occurred in 36 (95% CI, 34–38) cases per 100,000 person-years, and the median survival from cancer diagnosis was 0.6 years (interquartile range, 0.2–1.6). Participants with a negative upper endoscopy had a 61% decreased risk of mortality in upper gastrointestinal cancer compared with those without an upper endoscopy (adjusted HR, 0.39; 95% CI, 0.37–0.42). The adjusted HRs were more pronounced during the first years of follow-up, but a risk reduction remained for at least 10 years (Figure 3). The sensitivity analysis when a negative endoscopy was redefined as without any upper gastrointestinal cancer or preneoplastic lesion showed a risk reduction of

Table 3. Risk of Upper Gastrointestinal Cancer After a Negative Screening Upper Endoscopy, Excluding All Premalignant Findings

Variable	Person-years, n	Cases, n	Incidence rate[a]	Unadjusted HR (95% CI)	Adjusted[b] HR (95% CI)
Negative upper endoscopy					
No	2,818,272	2713	96.3	1.00 (Reference)	1.00 (Reference)
Yes	4,009,364	1277	32.9	0.44 (0.41–0.47)	0.46 (0.43–0.49)

[a]Per 100,000 person-years
[b]Adjusted for sex, age, calendar year, Charlson comorbidity index, and country.

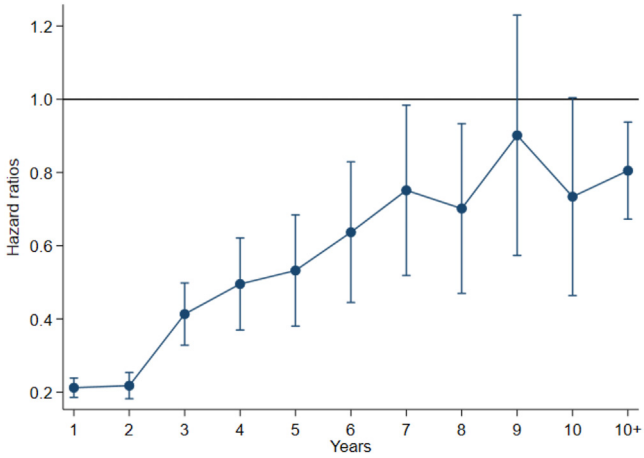

Figure 3. Adjusted mortality in upper gastrointestinal cancer by year of follow-up after a negative upper endoscopy in patients with GERD.

death due to upper gastrointestinal cancer similar to that of the main analysis (adjusted HR, 0.37; 95% CI, 0.34–0.41).

Incidence and Mortality Due to Esophageal Adenocarcinoma

From the patients with GERD without an upper endoscopy, 1261 (0.12%) new cases of esophageal adenocarcinoma occurred and 1036 patients (0.10%) died due to esophageal adenocarcinoma during follow-up. The corresponding numbers in patients with a negative upper endoscopy were 692 (0.09%) and 522 (0.07%). Comparing the negative upper endoscopy group with those without a negative endoscopy, the risk of developing esophageal adenocarcinoma was 50% decreased (adjusted HR, 0.50; 95% CI, 0.45–0.55) and the risk of mortality due to esophageal adenocarcinoma was 67% decreased (adjusted HR, 0.33; 95% CI, 0.30–0.37).

Discussion

The main finding of this study was that an upper endoscopy with negative findings in patients with GERD was associated with a reduced incidence and mortality rates of any upper gastrointestinal cancer and in esophageal adenocarcinoma analyzed separately. The risk reductions in incidence and mortality lasted for 5 years and 10 years, respectively.

To our knowledge, this is the largest study to date assessing the role of upper endoscopy for GERD in relation to the incidence and mortality of upper gastrointestinal cancer. It is also the first study examining the durability of these risk reductions. Methodological strengths of the study include the use of well-validated and prospectively collected data from nationwide complete registries, which mitigated misclassification of exposures and outcomes and provided an unselected cohort with complete follow-up. The large sample size collected from 4 entire countries allowed for precise subgroup analyses throughout the follow-up.

Limitations of this study are mainly related to its observational design. Residual confounding by variables related to the outcomes and the propensity of receiving an upper endoscopy cannot be excluded, for example, tobacco smoking, alcohol consumption, and obesity. These variables were partly controlled for by the adjustment for the Charlson Comorbidity Index, which includes diseases closely associated with these exposures, but were not possible to directly assess. The propensity of receiving an endoscopy may also be a marker for increased engagement with health care and correspond to healthier lifestyle habits, whereas frailer patients may refrain from endoscopy. Such variables and behaviors were not possible to account for, but are unlikely to explain the strong observed associations between a negative endoscopy and upper gastrointestinal cancer. GERD patients who underwent upper endoscopy likely presented with more severe or more alarming symptoms and may thus have an increased risk of upper gastrointestinal cancer compared with the patients without endoscopy. However, this issue would not explain any associations, but would instead lead to an underestimation of the protective influence of a negative upper endoscopy and upper gastrointestinal cancer. It should also be noted that the GERD diagnosis was based on International Classification of Diseases codes determined by a specialist. Therefore, the results should not be inferred on the general public with mild symptoms of reflux, but rather to those seeking specialized medical advice and treatment. The study therefore took place under ubiquitous and uniform antireflux therapy, where validation studies of this cohort found that 90% of patients were prescribed a proton pump inhibitor within 3 months of GERD diagnosis.[14]

It was not surprising to find that a negative upper endoscopy resulted in a pronounced and durable risk reduction in upper gastrointestinal cancer incidence and

mortality. Similar results have been found after a negative colonoscopy for colorectal cancer.[15] Similar to colonoscopy screening, upper endoscopy can reduce cancer incidence through the detection and treatment of premalignant lesions, such as intestinal metaplasia with dysplasia and adenomas, and prevent mortality through earlier tumor detection, which allows for curatively intended treatment. For example, endoscopic treatment of dysplastic Barrett's esophagus decreases the risk of progression to esophageal adenocarcinoma, removal of gastric or duodenal adenomas decreases the risk of cancer development, and eradication of *Helicobacter pylori* infection reduces the risk of gastric cancer.[16–20] Thus, early identification and treatment of premalignant lesions and risk factors for upper gastrointestinal cancer through upper endoscopy in patients with GERD is likely to decrease the incidence and mortality in upper gastrointestinal cancer.

The decreased risk of developing upper gastrointestinal cancer after a negative upper endoscopy was particularly evident within the first year of follow-up, and then approached the incidence of the participants without endoscopy. Such a relatively rapid return to the baseline risk has not been observed in patients undergoing colonoscopy screening, but was still well in line with what is to be expected because new tumors can start to arise after 1 year and onward. The return to the baseline risk might reflect that some early premalignant or malignant lesions remained unrecognized at endoscopy. A meta-analysis indicated that 11% of incident upper gastrointestinal cancers were missed during a previous upper endoscopy, indicating the importance of quality control in upper endoscopy.[21] Reviews of patients diagnosed with upper gastrointestinal cancer a short time after a negative upper endoscopy found that the index upper endoscopy in most of these patients demonstrated suspicious or unclear findings that were neglected by the endoscopist or the reviewing pathologist.[22,23] Approximately 30% of esophageal adenocarcinomas arising from Barrett's esophagus are now considered to be post-endoscopy tumors.[24] Regarding colonoscopy, several quality indicators have been developed and implemented after the introduction of general colorectal cancer screening programs, such as adenoma detection rate of the performing endoscopist.[25] Although there are some potential quality indicators for upper endoscopy, that is, rate of targeted biopsies, procedure time, and, more recently, the use of computer-aided detection, the relevance of these indicators in relation to cancer outcomes is still largely unknown. Nevertheless, we found a more pronounced risk reduction in the more recent calendar period, which may be interpreted as a result of higher-quality endoscopy procedures.

Most previous studies that have assessed upper endoscopy in relation to the risk of upper gastrointestinal cancer have analyzed gastric or esophageal tumors separately. However, it makes sense to analyze upper gastrointestinal cancer together because routine upper endoscopy assesses the entire upper gastrointestinal tract. Among the few studies that have examined the risk of all upper gastrointestinal cancer in patients after a negative upper endoscopy was a US Department of Veterans Affairs study of 68,610 patients with GERD. During a mean follow-up of 3 years after endoscopy, the incidence rate of cancer was 13 per 100,000 person-years (n = 29), that is, considerably lower than the incidence rate observed in this study.[22] However, that study was limited by short follow-up, low statistical power, and it did not have an unscreened comparison group for the assessment of incidence rate and mortality rate ratios of upper gastrointestinal cancer. There is some other indirect evidence supporting that upper endoscopy may prevent upper gastrointestinal cancer. A study from the United Kingdom indicated that a higher rate of referral for endoscopy (for any indication) in routine clinical practice was associated with decreased mortality and increased likelihood of curative treatment for upper gastrointestinal cancer.[26] A Korean study found that upper endoscopic screening may reduce mortality in gastric cancer by 40%, indicating the benefit of upper endoscopy in high-risk populations.[27] Other studies have suggested that a negative endoscopy within a certain time frame before esophageal adenocarcinoma diagnosis improves survival.[28,29] However, none of these studies addressed whether upper endoscopy for upper gastrointestinal cancer is beneficial in patients with GERD.

The relatively low incidence of esophageal and gastric cancer in Western populations compared with that in many Eastern populations has contributed to preventing widespread implementation of endoscopic screening for these tumors in Western countries. In the present study, however, the incidence rate of upper gastrointestinal cancer in patients with GERD was comparable with the incidence rate of colorectal cancer in the general US population aged 60–69 years, for whom colonoscopy screening is recommended.[30] The lower age limit to commence screening for colorectal cancer was recently reduced to 45 years, when the incidence is lower (31 per 100,000).[31] Landmark studies have demonstrated that a colonoscopy with negative findings or polypectomy for colonic adenomas is associated with decreased mortality in colorectal cancer, which has contributed to the implementation of colonoscopy screening.[32,33] A negative colonoscopy may be followed by a period of 10 years of reduced incidence and mortality in colorectal cancer.[15,34,35] The present study indicates that upper endoscopy may be beneficial for patients with GERD, but to make upper endoscopy screening more cost-beneficial at its initiation, the target group may be limited to include patients at highest risk of cancer. Such previous cost-effectiveness studies have indicated that endoscopy is cost-effective in men at aged 50 years or older with chronic GERD.[36,37] In time, screening may also move from endoscopy, which often requires sedation and access to a specialized gastroenterologist or surgery to department, toward less invasive alternatives. The use of, for example, breath tests and swallowable esophageal cell collection devices with biomarkers, which can be administered in the primary care setting, may even be cost-effective in people 50 years or older independent of GERD symptoms.[36] A main drawback of these less invasive methods compared with endoscopy is the inability to directly and exactly assess any pathological lesions.

This study was based on nationwide data from 4 Nordic countries, which should ensure that the results are generalizable to other Western populations. However, the replication of this study in other populations is important, given the considerable geographical variations in the incidence of upper gastrointestinal cancer.[38]

In conclusion, this population-based study from 4 Nordic countries indicates that patients with GERD with a negative upper endoscopy have a decreased incidence and mortality in upper gastrointestinal cancer for 5 and 10 years. The more pronounced risk reduction from year 2008 onward indicates a powerful protective effect of higher-quality upper endoscopies in a modern setting. The relatively high incidence rate of upper gastrointestinal cancer in patients with GERD indicates that a 1-time upper endoscopy may be beneficial.

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.2021.10.003.

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Supplementary Table 1. Definition of Gastroesophageal Reflux Disease in the Nordic Countries

ICD version	ICD codes[a]
7	530.90, 539.11, 539.12, 560.40, 551.30, 551.39, 784.30, 784.39
8	78430, 55130, 53093, 53094
9	7871A, 787B, 5513A, 553D, 530B–C, 5301A–D, 5301X
10	K20, K21, K22.7, K44, R12

ICD, International Classification of Diseases.
[a]Danish ICD-10 codes start with the letter "D"; otherwise they are identical to standard ICD-10.

Supplementary Table 2. Definition of Upper Endoscopy in the Nordic Countries

	Operation classification before 1997			
Variable	Denmark: operations–*og behandlingsklassifikation, Sundhedstyrelsen,* 1988	Finland: T*oimenpidenimikkeistö*, 1983	Sweden: *Klassifikation av operationer*	Operation classification from 1997, NOMESCO[a]
Upper endoscopy with or without biopsy	9101	1300, 1310	4480, 9004	UJD02, UJD10

NOMESCO, Nordic Medico-Statistical Committee.
DK, Denmark; FI, Finland; ICD, International Classification of Diseases.
[a]Danish NOMESCO codes start with the letter "K"; otherwise they are identical to standard NOMESCO.

Supplementary Table 3. Definition of Endoscopic and Surgical Treatment of Esophagus or Stomach in the Nordic Countries

Variable	Operation classification before 1997			Operation classification from 1997, NOMESCO[a]
	Denmark: operations–*og behandlingsklassifikation, Sundhedstyrelsen*, 1988	Finland: *Toimenpidenimikkeistö*, 1983	Sweden: *Klassifikation av operationer*	
Operations for GERD				
Operation for diaphragmatic hernia (including fundoplication)	4054; 4056; 4074; 4076; 4080; 4084	5884, 6241; 6242; 6249; 6251; 6259	427	JBB; JBC; JBW
Operations on esophagus				
Resection of esophagus	4106; 4108	6201–6209	282	JCC
Esophagostomy	4114	6216, 6302	283	JCB
Anastomosis of esophagus without resection	4114; 4146; 4148; 4150	6233–6236	284	JCD
Reconstruction of esophagus	4104; 4120; 4122; 4124; 41280; 41285; 4116	6213, 6217	285	JCE
Other operations on esophagus, including local operations	4102; 4110; 4112; 4130; 4138; 4140; 4169; 41601	6211–6212, 6214–6215, 6218–6229, 6231, 6239, 6302, 6304	280; 281; 286; 287	JCW; JCF
Operations on stomach				
Resection of stomach (including partial gastrectomy)	4188; 4192; 4194; 4196; 4198; 4200; 4210; 4214	6301, 6311, 6313–6321, 6329	442	JDC
Total gastrectomy	4218	6322, 6323	443	JDD
Gastrostomy	4176	6312	444	JDB
Anastomosis of stomach	4222; 4224; 4226; 4228; 4233	6331, 6332	445	JDE
Vagotomy	4262; 4268; 4272; 4274	6351–6359	447	JDG
Other operation on stomach or duodenum	4174; 4179; 4180; 4181; 4184; 4189; 4219; 42331; 4238; 4244; 4246; 4248; 4299; 4280	6309,6333–6339, 6361–6369 6371–6379, 6521	440; 446; 441; 449	JDH, JDW
Bariatric surgery	NA	6548, 6559	475	JDF

NA, not available (not defined in the classification system); NOMESCO, Nordic Medico-Statistical Committee.
[a]Danish NOMESCO codes start with the letter "K"; otherwise, they are identical to standard NOMESCO.

Supplementary Table 4. Definition of Preventive Endoscopic Treatment of Esophagus or Stomach in the Nordic Countries

	Operation classification before 1997			
Variable	Denmark: operations–*og behandlingsklassifikation, Sundhedstyrelsen*, 1988	Finland: *Toimenpidenimikkeistö*, 1983	Sweden: *Klassifikation av operationer*	Operation classification from 1997, NOMESCO[a]
Polypectomy in esophagus	NA	1321, 1301, 1311	2891	JCA05
Polypectomy in stomach	NA	1301, 1311	4486	JDA05
Mucosal or submucosal resection in esophagus	NA	NA	NA	JCA45
Mucosal or submucosal resection in stomach	NA	NA	NA	JDA45
Procedure using diathermy or heat in esophagus (RFA)	NA	NA	NA	JCA52

NA, not available (not defined in the classification system); NOMESCO, Nordic Medico-Statistical Committee; RFA, radiofrequency ablation.
[a]Danish NOMESCO codes start with the letter "K"; otherwise, they are identical to standard NOMESCO.

Supplementary Table 5. Definition of Premalignant Lesions of Esophagus or Stomach in the Nordic Countries

Variable	ICD-7	ICD-8 (DK)	ICD-8	ICD-9 (FI)	ICD-9	ICD-10
Barrett's esophagus	—	—	—	5501B	—	K227
Crohn's disease	572	563	563	555	555	K50
Esophageal, gastric, or duodenal adenoma	21100; 21110; 21120	21109; 21119; 21120	21100; 21110; 21121	2110A–X; 5378C; 2111A-X; 2112A-X	211A; 211B; 211C	D130; D131; D132
Peptic ulcer in stomach or duodenum	540; 541; 542	531; 532; 533; 534	531; 532; 533; 534	531, 532	531; 532; 533	K25; K26; K27
Chronic atrophic gastritis	54301	53503	53503	5351A; 5351B: 5351C; 5351D; 5351X	535B	K294

DK, Denmark; FI, Finland; ICD, International Classification of Diseases.

Supplementary Table 6. Definition of Upper Gastrointestinal Cancer in the Nordic Countries

Variable	ICD-8 (DK)	ICD-8 (SWE)	ICD-9 (FIN)	ICD-9 (SWE)	ICD-9 (INT)	8ICD-10
Esophageal cancer	150; 15109	150; 15101	150; 1510 (A-X)	150; 1510	150, 1510	C15; C160
Gastric cancer	15119; 15180; 15181; 15189; 15199	15111, 15181, 15187, 15199	1511-1519 (A-X)	1511; 1513; 1514; 1518; 1519	1511; 1512; 1513; 1514; 1515; 1516; 1518; 1519; 20963	C161; C162; C163; C164; C165; C166; C168; C169.
Duodenal cancer	15209	15201	1520 (A-X)	1520	1520; 20901	C170

DK, Denmark; FIN, Finland; ICD, International Classification of Diseases; INT, International; SWE, Sweden.