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HELICOBACTER PYLORI

Risk of Esophageal Adenocarcinoma After *Helicobacter pylori* Eradication Treatment in a Population-Based Multinational Cohort Study

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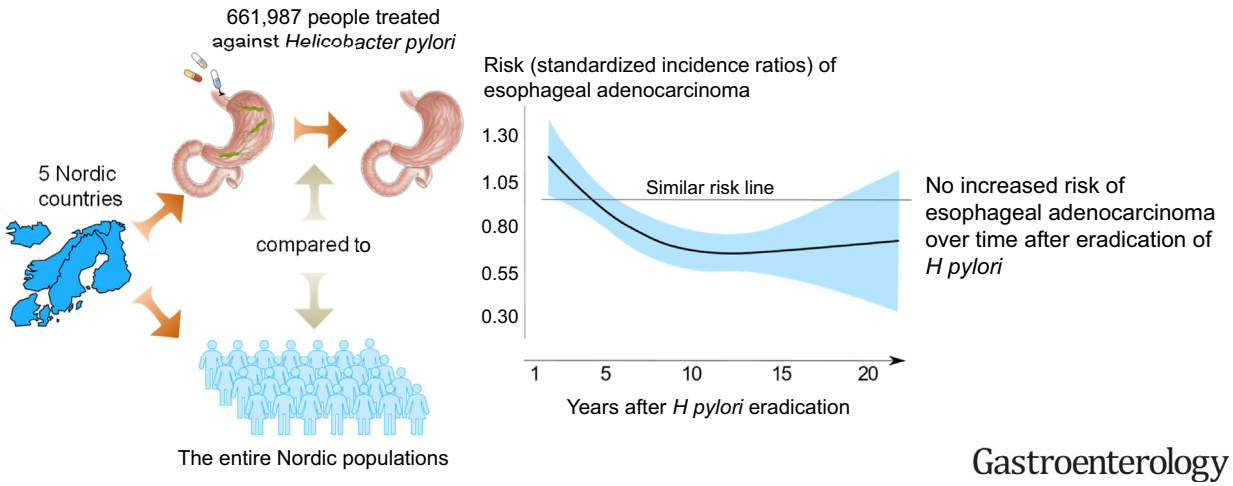
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e14. Learning Objective: Upon completion of this CME activity, successful learners will be able to explain the association between infection with *Helicobacter pylori* and developing esophageal cancer, and how eradication of this infection influences this risk.



BACKGROUND & AIMS: *Helicobacter pylori* infection is associated with a decreased risk of esophageal adenocarcinoma, and the decreasing prevalence of such infection might contribute to the increasing incidence of this tumor. We examined the hypothesis that eradication treatment of *H pylori* increases the risk of esophageal adenocarcinoma. **METHODS:** This population-based multinational cohort, entitled "Nordic *Helicobacter Pylori* Eradication Project (NordHePEP)," included all adults (≥18 years) receiving *H pylori* eradication treatment from 1995–2018 in any of the 5 Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) with follow-up throughout 2019. Data came from national registers. We calculated standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) by dividing the cancer incidence in the exposed cohort by that of the entire Nordic background populations of the corresponding age, sex, calendar period, and country. Analyses were stratified by factors associated with esophageal adenocarcinoma (ie, education, comorbidity, gastroesophageal reflux, and certain medications). **RESULTS:** Among 661,987 participants who contributed 5,495,552 person-years after eradication treatment (median follow-up, 7.8 years; range, 1–24 years), 550 cases of esophageal adenocarcinoma developed. The overall SIR of esophageal adenocarcinoma was not increased (SIR = 0.89; 95% CI, 0.82–0.97). The SIR did not increase over time after eradication treatment, but rather decreased and was 0.73 (95% CI, 0.61–0.86) at 11–24 years after treatment. There were no major differences in the stratified analyses. The overall SIR of esophageal squamous cell carcinoma, calculated for comparison, showed no association (SIR = 0.99; 95% CI, 0.89–1.11). **CONCLUSIONS:** This absence on an increased risk of esophageal adenocarcinoma after eradication treatment of *H pylori* suggests eradication is safe from a cancer perspective.

Keywords: Eradication; *Helicobacter pylori*; Esophageal Cancer; Esophageal Neoplasm; Multinational.

Esophageal cancer is the 7th most common cancer and the 6th most common cause of cancer death globally and is characterized by demanding treatment and poor survival.[1,2] The incidence of esophageal adenocarcinoma has increased markedly during the last 4 decades, especially in high-income countries, where it has surpassed the incidence of esophageal squamous cell carcinoma, the other main histologic type of esophageal cancer.[3,4] This increase might be due in part to the decreasing prevalence of infection with the stomach bacterium *Helicobacter pylori* because this infection is associated with a decreased risk of esophageal adenocarcinoma, but not esophageal squamous cell carcinoma.[5–7] *H pylori* typically infects humans in early childhood and has a global prevalence of >50%, ranging from 20% in high-income regions to 85% in developing countries.[8] Infection can cause duodenal or gastric ulcers, which is the main indication for eradication treatment. It can also lead to gastric atrophy and the development of noncardia gastric cancer, which is counteracted by eradication.[9–12] Therefore, *H pylori* should be treated if detected. The decreased risk of esophageal adenocarcinoma seen in individuals with *H pylori* infection is probably explained by the *H pylori*–induced gastric atrophy, which reduces gastric acid production and thus acidic gastroesophageal reflux, the main risk factor for this tumor.[13,14] It seems plausible that eradication of *H pylori* would increase the risk of esophageal adenocarcinoma, although the answer to this question is unknown with the only study on the topic (from our group) having too few cases and too short follow-up.[15] If eradication treatment of *H pylori* increases the risk of esophageal adenocarcinoma, this should be taken into account when considering such treatment in patients and populations.

The aim of this study was to test the hypothesis that *H pylori* eradication treatment gradually increases the risk of esophageal adenocarcinoma over time after treatment.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Helicobacter pylori infection is associated with a decreased risk of esophageal adenocarcinoma, but it is unknown if eradication treatment of this bacterium increases the risk of this tumor.

NEW FINDINGS

Participants who received eradication treatment had no increased risk of esophageal adenocarcinoma compared with the corresponding background population, and the risk estimates did not increase over time after treatment.

LIMITATIONS

Some level of misclassification of the eradication treatment and the exact tumor site as well as residual confounding cannot be excluded in this observational study.

CLINICAL RESEARCH RELEVANCE

The absence of an increased risk of esophageal adenocarcinoma after eradication treatment of *H pylori* suggests that such eradication is safe from a cancer perspective. Thus, eradication treatment of *H pylori* for the purpose of preventing gastric cancer may not lead to any increased risk of esophageal adenocarcinoma.

BASIC RESEARCH RELEVANCE

The biologic mechanisms behind the lack of an increased risk of esophageal adenocarcinoma after eradication treatment of *H pylori* need to be explored in future research.

Methods

Design

This was a population-based and multinational cohort study with a total study period spanning from 1995 until the end of 2019. To be able to examine how the exposure to *H pylori* eradication treatment influences the risk of esophageal adenocarcinoma, we created a large exposed cohort, entitled the "Nordic *Helicobacter Pylori* Eradication Project (NordHePEP)," which has been described in detail in a cohort profile paper.[16] In brief, this cohort consists of all adult individuals (aged 18 years or more) living in any of the 5 Nordic countries (ie, Denmark, Finland, Iceland, Norway, and Sweden [alphabetic order]), having dispensed at least 1 prescription of *H pylori* eradication treatment. Using the personal identity number uniquely assigned to all citizens of the Nordic countries, individuals' data were retrieved from and linked between well-maintained national registers. These registers included information about prescribed medications, cancer, diagnoses and procedures, mortality, and total national population. All these registers have nationwide complete coverage, virtually complete recording, and high validity.[16] The comparison cohort was the general population of all 5 Nordic countries of the corresponding age, sex, calendar period, and country as the exposed cohort. Ethical and data permissions were obtained from the relevant authorities within each country.[16]

Exposure

The study exposure was eradication treatment of *H pylori* recorded in a Nordic prescribed drug register. The eradication treatment consisted of a minimum 7-day regimen with a proton pump inhibitor combined with at least 2 of the antibiotics amoxicillin, clarithromycin, or metronidazole. This is the dominating regimen in the Nordic countries, accomplishing successful eradication in 79%–95% of infected individuals.[17–19] These medications are not sold over-the-counter in any of the countries and are thus completely recorded in the prescribed drug registers. By the fact that the prescribed drug registries are nationwide complete, the study includes all individuals having received *H pylori* eradication treatment in any of the

Abbreviations used in this paper: **CI, confidence interval; NordHePEP, Nordic *Helicobacter Pylori* Eradication Project; SIR, standardized incidence ratio.**

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entire populations of the 5 countries during the study period. Repeated eradication prescriptions dispensed within 12 months of an earlier prescription in the same individual were regarded as unsuccessful. In these cases, the date of eradication was set to the most recent treatment. Patients with less than 12 months of follow-up after the first recorded eradication treatment were excluded. Individuals with repeated eradication treatments more than 12 months apart were considered reinfected, and were excluded in sensitivity analyses (explained later in this article). The exposure period started when the participating countries' prescribed drug registers were initiated (ie, 1995 for Denmark and Finland, 2003 for Iceland, 2004 for Norway, and in 2005 for Sweden), and ended depending on the end of data availability in the prescribed drug register, cancer register, or cause of death register (ie, end of 2017 for Finland or end of 2018 for the other 4 countries). Cohort participants were only compared with the background population of their own country.

Outcome

The outcome was esophageal adenocarcinoma, including adenocarcinoma of the gastroesophageal junction. These tumors are commonly grouped because of anatomic proximity with difficulties separating them, combined with similar epidemiologic, histologic, and genetic features.[20] Esophageal squamous cell carcinoma was also analyzed, but only to assess the validity of the findings for esophageal adenocarcinoma, because there is no association between *H pylori* infection and squamous cell carcinoma and, therefore, no association with eradication treatment was expected. Individuals were excluded from the cohort if they had a history of esophageal cancer (adenocarcinoma or squamous cell carcinoma) before eradication treatment. To avoid detection bias, patients diagnosed with esophageal cancer within 12 months after eradication were excluded, which is common practice in similar studies. Patients diagnosed with esophageal adenocarcinoma (and squamous cell carcinoma) during follow-up of NordHePEP and the general population were identified by the national cancer registers (Supplementary Table 1).[16]

Statistical Analysis

Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) were calculated as the ratio of the observed number of patients with newly diagnosed esophageal adenocarcinoma (or squamous cell carcinoma) among the exposed cohort and the expected number of such cases. The expected number was derived from the incidence in the entire Nordic populations of the corresponding age (5-year categories), sex (men and women), calendar period (1995–1999, 2000–2004, 2005–2009, 2010–2014, and 2015–2018), and country (Denmark, Finland, Iceland, Norway, and Sweden). Cohort participants were followed up from 1 year after eradication treatment until the occurrence of esophageal cancer, death, emigration, or end of study period, whichever came first. To assess changes in risk over time after eradication treatment, analyses were stratified by 3 follow-up periods: 1–5, 6–10, and 11–24 years after treatment. Time trends in SIRs were also generated using Poisson regression models defining the number of events as the outcome, splines of time as the covariate, and expected events in the background population as the offset variable. The number of knots for the spline of time was assessed by comparing the Akaike's information criterion of models with different numbers of knots. The CI was estimated using a sandwich estimator of the variance.

In addition to the standardization for sex, age, calendar period, and country, analyses were stratified by 6 factors associated with the risk of esophageal adenocarcinoma: education ($\leq$9 years or $>$9 years, recorded in a national population register before eradication treatment), comorbidity (using the most well-validated version of the Charlson comorbidity index[21] score of 0, 1, or $\geq$2, recorded in a national patient register within 5 years before eradication treatment[16]), gastroesophageal reflux disease (any of the diagnoses heartburn, hiatal hernia, esophagitis, gastroesophageal reflux disease, or Barrett's esophagus recorded in a national patient register within 5 years before eradication treatment [#tblS2]), long-term medication with proton pump inhibitors,[22] nonsteroidal anti-inflammatory drugs,[23] and statins.[24] Long-term medication was defined as prescription of $>$180 tablets recorded in a Nordic prescribed drug register within 12 months before eradication treatment (Supplementary Table 3).

Sensitivity analyses were performed to identify possible misclassification of the exposure or outcome. Regarding the exposure, we first excluded participants defined as having been reinfected. Second, we excluded participants with reinfection close in time to eradication treatment (ie, during either 12–24 months or 12–36 months after treatment) and, therefore, potentially misclassified as reinfected when in fact it was unsuccessfully eradicated. Regarding the outcome, adenocarcinoma of the gastroesophageal junction was excluded in a sensitivity analysis. Due to regulations in Denmark, we were not allowed to report the results of less than 4 individuals. All data management and analysis followed a predefined study protocol, using Stata 16.1/17.0, and were led by a senior biostatistician (G.S.).

Patient and Public Involvement

We collaborated with a patient research partnership group consisting of former esophageal and gastric cancer patients. They were involved when we came up with the idea of creating this cohort and conducting this specific study and how is was designed. They have given their full support for this study, but were not directly involved in the conduction of the study.

Role of the Funding Source

This study was supported by the Sjoberg Foundation (2021-01-14:9), Nordic Cancer Union (R278-A15884), Stockholm County Council (501242 and FoUI-963792), and Stockholm Cancer Society (201163). None of the funding sources had any role in the study's design, conduct, and reporting.

Results

Cohort Participants

The exposed cohort included 661,987 patients having received *H pylori* eradication treatment. The median follow-up was 7.8 years (range, 1–24 years) and the participants contributed 5,495,552 person-years at risk. Characteristics of the study participants are presented in Table 1. The majority were women (54.3%), aged $\leq$60 years (57.2%),

Table 1. Participants With Eradication Treatment of *H pylori*

Characteristic	No. (% of total cohort)
Total cohort	661,987 (100.0)
Sex	
Men	302,404 (45.7)
Women	359,583 (54.3)
Country	
Denmark	145,914 (22.0)
Finland	266,422 (40.2)
Iceland	8032 (1.2)
Norway	58,684 (8.9)
Sweden	182,935 (27.6)
Age (*y*)	
18–30	59,178 (8.9)
31–40	82,616 (12.5)
41–50	112,664 (17.0)
51–60	138,743 (21.0)
61–70	134,113 (20.3)
71–80	96,813 (14.6)
>80	37,860 (5.7)
Calendar period	
1995–1999	48,211 (7.3)
2000–2004	125,151 (18.9)
2005–2009	186,607 (28.2)
2010–2014	177,345 (26.8)
2015–2018	124,673 (18.8)
Education (data available for Denmark and Sweden)	
≤9 y	114,385 (34.8)
>9 y	191,802 (58.3)
Missing	22,662 (6.9)
Charlson comorbidity index	
0	497,948 (75.2)
1	95,089 (14.4)
≥2	37,990 (5.7)
Missing	30,960 (4.7)
Gastroesophageal reflux disease[a]	
Total	48,608 (7.3)
Heartburn	920 (0.1)
Hiatal hernia	25,072 (3.8)
Gastroesophageal reflux disease	13,066 (2.0)
Esophagitis	18,375 (2.8)
Barrett's esophagus	763 (0.1)
Long-term medication[b]	
Proton pump inhibitors	70,724 (10.7)
Nonsteroidal anti-inflammatory drugs	80,151 (12.1)
Statins	76,044 (11.5)
Follow-up	
Median (interquartile range; *y*)	7.8 (3.8–12.3)
Person-years at risk	5,495,552
Reinfection[c]	46,453 (7.0)

[a]Recorded in a patient register within 5 y before eradication treatment of *H pylori*.
[b]>180 tablets prescribed within 1 y before eradication treatment of *H pylori*.
[c]Additional *H pylori* eradication prescription(s) >12 mo after an earlier treatment.

and without serious comorbidity (75.2% with Charlson comorbidity index 0). Gastroesophageal reflux disease within 5 years before eradication treatment was recorded in 7.3% of the participants. The frequencies of long-term medication with proton pump inhibitors were 10.7%, nonsteroidal anti-inflammatory drugs 12.1%, and statins 11.5%. The *H pylori* reinfection rate was 7.0%.

Esophageal Adenocarcinoma

A total of 550 participants developed esophageal adenocarcinoma during follow-up of the exposed cohort after *H pylori* eradication treatment (Table 2). The overall SIR was not increased (SIR, 0.89; 95% CI, 0.82–0.97), irrespective of sex or age group. The SIR instead tended to decrease with longer follow-up time and was 0.73 (95% CI, 0.61–0.86) after 11–24 years of eradication treatment (Table 2). The Poisson regression estimation also indicated a decrease in the SIR, which seemed to plateau approximately 8 years after eradication treatment (Figure 1).

In stratified analyses, none of the subgroups showed increasing SIRs over time after eradication treatment (Table 3). Similarly, the country-specific analyses did not reveal any increased SIRs with longer follow-up after treatment (Table 4). An overall increased SIR of esophageal adenocarcinoma was found among participants with gastroesophageal reflux disease and in those using long-term proton pump inhibitors. Differing trends over follow-up time after *Helicobacter* eradication treatment between strata were found in long-term users of proton pump inhibitors and in patients with less education, which had a persistently increased risk of esophageal adenocarcinoma after eradication treatment, whereas nonusers of proton pump inhibitors and participants with longer education showed decreasing SIRs. The pattern of decreasing SIRs over time after eradication treatment was also found in all strata of comorbidity, gastroesophageal reflux disease, and long-term medication with nonsteroidal anti-inflammatory drugs and statins.

The sensitivity analyses excluding reinfected patients showed similar SIRs as in the main analysis (Supplementary Table 4), and the sensitivity analyses excluding adenocarcinoma of the gastroesophageal junction did not alter the results (Supplementary Table 5).

Esophageal Squamous Cell Carcinoma

Esophageal squamous cell carcinoma occurred in 323 participants after eradication treatment, corresponding to a SIR of 0.99 (95% CI, 0.89–1.11).

Discussion

This study found no evidence supporting the hypothesis of a gradually increasing risk of esophageal adenocarcinoma over time after *H pylori* eradication treatment.

Methodologic strengths of the study include the population-based design with complete participation, the large number of study participants having received *H pylori*

Table 2. Risk of Esophageal Adenocarcinoma After Eradication Treatment of *H pylori* Compared With the Corresponding General Nordic Population

	Esophageal adenocarcinoma	
	Observed vs expected no. of cases	SIR (95% CI)
Total	550 vs 617	0.89 (0.82–0.97)
Sex		
Men	414 vs 484	0.86 (0.78–0.94)
Women	136 vs 133	1.02 (0.86–1.21)
Age at eradication treatment (*y*)		
≤55	142 vs 142	1.00 (0.84–1.18)
>55	408 vs 475	0.86 (0.78–0.95)
Years after eradication treatment		
1–5	244 vs 217	1.12 (0.99–1.27)
6–10	170 vs 212	0.80 (0.69–0.93)
11–24	136 vs 188	0.73 (0.61–0.86)

eradication treatment, and the long (up to 24 years) and complete follow-up. The national register data of the 5 Nordic countries have similar contents and structure, high quality, and completeness. The combining of the register data with the personal identification number system in these countries enabled tracking of each exposed patient and allowed linkages of each individual's data. The lack of association between *H pylori* eradication treatment and esophageal squamous cell carcinoma was expected due to the lack of association between infection and this tumor, and this supports the validity of the study and thus the trustworthiness of the results for esophageal adenocarcinoma.

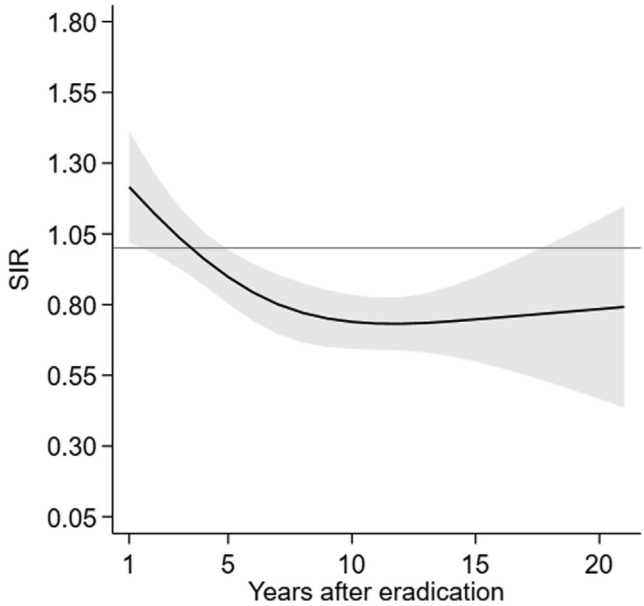

Figure 1. Risk of esophageal adenocarcinoma over time after eradication treatment of *H pylori* (x-axis) compared with the corresponding general populations of the 5 Nordic countries, presented as SIRs (y-axis) with 95% CIs (shaded area) using Poisson regression.

Among weaknesses is potential exposure misclassification. The background population used as the comparison cohort consists of both infected (about 20%) and noninfected individuals,[25] as well as the patients included in the exposed cohort. This could dilute the results, but not explain the lack of increased risk of esophageal adenocarcinoma over time after treatment. An ideal control group would be *H pylori*–infected persons who did not have eradication, but this would not be feasible or ethically justified, and using the corresponding background population is a valid comparator. There is some uncertainty associated with patient compliance with the *H pylori* eradication treatment. However, the cohort inclusion criteria required formal prescription by a physician as well as dispensation of and payment for the medications at a pharmacy, which increase compliance. We did not have access to diagnostic test results of the success of the eradication treatment. Additionally, some level of antibiotic resistance exists for the triple therapy, although a recent large study reported lower resistance rates in northern Europe compared with the rest of Europe, at 10.2% for clarithromycin, resulting in an overall eradication rate of almost 90% in 2018,[26] and country-specific studies showing clarithromycin resistance at 15% in Sweden,[18] and 95% eradication success in Denmark.[27] Therefore, it should be stressed that the study examined eradication treatment rather than proven eradication, although successful eradication may be assumed unless additional eradication treatments are prescribed.[28] The rather high reinfection rate of 7% might include patients with false ascertainment of prior eradication. To assess if reinfection influenced the results, we performed sensitivity analyses excluding assumed reinfected participants, and the unchanged results were reassuring. Any potential eradication treatment before the start of the study could not be taken into account. To avoid bias from the inclusion of patients in the eradication treatment cohort at different time points in the participating countries, patients who underwent eradication treatment in one country were only compared with the corresponding background population of that country during the same calendar period. The median follow-up of 7.8 years may be considered short, but many patients within this large cohort study had a much longer follow-up (up to 24 years) and the results for the follow-up category 11–24 years had good statistical precision. There is a level of tumor misclassification regarding the exact site of adenocarcinoma of the distal esophagus, gastroesophageal junction, and proximal stomach.[29] However, 2 comprehensive validation studies of the Swedish Cancer Registry have found that tumor misclassification is an issue between esophageal and cardia adenocarcinoma and between distal and cardia gastric adenocarcinoma, but not between esophageal and distal gastric adenocarcinoma.[29,30] Moreover, the fact that the exclusion of cardia adenocarcinomas in the sensitivity analyses did not change the results argues against misclassification of distal

Table 3. Risk of Esophageal Adenocarcinoma After Eradication Treatment of *H pylori* Compared With the General Populations of the 5 Nordic Countries in Stratified Analyses

		SIR (95% CI), y after eradication treatment			
		1–24 y (total)	1–5 y	6–10 y	11–24 y
Education (data only available for Denmark and Sweden)					
≤9 y		1.01 (0.84–1.19)	1.18 (0.90–1.53)	0.85 (0.60–1.17)	0.96 (0.67–1.32)
>9 y		0.79 (0.67–0.92)	0.97 (0.75–1.23)	0.79 (0.59–1.03)	0.57 (0.40–0.80)
Charlson comorbidity index					
0		0.86 (0.78–0.95)	1.07 (0.91–1.25)	0.78 (0.65–0.93)	0.74 (0.61–0.89)
1		0.91 (0.74–1.11)	1.17 (0.88–1.53)	0.80 (0.54–1.14)	0.61 (0.34–1.00)
≥2		1.19 (0.88–1.58)	1.37 (0.93–1.94)	1.06 (0.58–1.77)	0.78 (0.21–1.99)
Gastroesophageal reflux disease[a]					
Yes		1.47 (1.16–1.83)	2.03 (1.46–2.75)	1.04 (0.63–1.63)	1.17 (0.67–1.90)
No		0.84 (0.76–0.92)	1.03 (0.89–1.18)	0.78 (0.66–0.91)	0.69 (0.57–0.83)
Long-term medication[b]					
Proton pump inhibitors	Yes	1.61 (1.29–2.00)	1.88 (1.39–2.49)	1.24 (0.79–1.86)	1.60 (0.85–2.73)
	No	0.82 (0.75–0.90)	1.02 (0.88–1.17)	0.76 (0.64–0.89)	0.69 (0.57–0.82)
Nonsteroidal anti-inflammatory drugs	Yes	0.93 (0.76–1.14)	1.07 (0.80–1.41)	0.93 (0.65–1.30)	0.56 (0.27–1.03)
	No	0.88 (0.80–0.97)	1.14 (0.98–1.30)	0.77 (0.65–0.92)	0.74 (0.62–0.88)
Statins	Yes	0.93 (0.79–1.16)	1.17 (0.87–1.54)	0.80 (0.52–1.18)	0.36 (0.10–0.92)
	No	0.89 (0.81–0.97)	1.11 (0.96–1.28)	0.80 (0.68–0.94)	0.75 (0.63–0.89)

[a]Recorded in a patient register within 5 y before eradication treatment of *H pylori*.
[b]>180 tablets prescribed within 1 y before eradication treatment of *H pylori*.

adenocarcinomas influencing the results for esophageal adenocarcinoma. The exclusion of adenocarcinoma of the gastroesophageal junction did not change the result, suggesting robustness. Detection bias could be a concern because eradication treatment is often associated with endoscopy and thus earlier tumor detection. To avoid this error, we excluded the first year of follow-up, which is common practice in studies like the present one. Residual confounding cannot be ruled out in observational studies, although we controlled for age, sex, calendar year, and country, used stratification for 6 other relevant factors, and performed several sensitivity analyses, all without showing any indications of confounding that would falsely conceal an increased risk of esophageal adenocarcinoma after eradication treatment. The statistical precision was a concern in the country-specific analyses of Iceland and Norway, because these countries contributed with few patients, particularly those with long follow-up. This could explain the seemingly higher risk estimates in these 2 countries compared with the other 3 countries that showed more homogeneous results, probably due to the much better statistical power.

H pylori infection of the stomach is a strong and causal risk factor for gastric cancer, and eradication treatment reduces this risk by approximately 50%.[11] On the other hand, the literature provides substantial evidence that this infection is associated with a strongly decreased risk of esophageal adenocarcinoma.[31] However, only one study has

Table 4. Country-Specific Risk of Esophageal Adenocarcinoma After Eradication Treatment of *H pylori* Compared With the General Populations of the 5 Nordic Countries

		SIR (95% CI), y after eradication of *H pylori*			
Country	No.	1–24 y (total)	1–5 y	6–10 y	11–24 y
Denmark	145,914	0.89 (0.78–1.02)	1.09 (0.87–1.36)	0.88 (0.68–1.12)	0.74 (0.57–0.94)
Finland	266,422	0.81 (0.70–0.93)	1.05 (0.83–1.31)	0.71 (0.54–0.91)	0.69 (0.52–0.9)
Iceland	8032	1.75 (0.84–3.22)	1.19 (0.24–3.47)	2.30 (0.74–5.37)	1.98 (0.22–7.14)
Norway	58,684	1.98 (1.45–2.63)	2.52 (1.67–3.64)	1.34 (0.69–2.34)	1.86 (0.68–4.05)
Sweden	182,935	0.79 (0.63–0.98)	0.97 (0.73–1.27)	0.66 (0.44–0.96)	0.46 (0.17–1.00)

attempted to assess the risk of esophageal adenocarcinoma after eradication treatment. This was our Swedish study showing an overall SIR of 1.26 (95% CI, 0.62–2.26), but was based on only 11 cases of esophageal adenocarcinoma and had only a short (up to 7.5 years) follow-up, and the risk estimates did not increase over time as hypothesized.[15] Moreover, there was a substantial risk of detection bias in that study because Barrett's esophagus is diagnosed using endoscopy, and those who had eradication therapy often underwent endoscopy. That study made us realize the need for this multinational investigation.

The present study showed no increased risk of esophageal adenocarcinoma over time after eradication treatment of *H pylori*, as hypothesized. The lack of increased risk may be due to that chronic gastric atrophy caused by *H pylori*,[32] which does not regress sufficiently to recover a physiological acid production enough to develop gastroesophageal reflux disease. The decreased SIRs of esophageal adenocarcinoma in the longest follow-up period suggest that patients having received eradication treatment for *H pylori* may have changed lifestyle habits due to the indication for such treatment (ie, mainly duodenal or gastric ulcers, which could have caused bleeding or even perforation). Patients with peptic ulcer disease are frequently recommended healthier lifestyle habits (eg, smoking cessation, dietary advice, and avoidance of heavy alcohol drinking). The increased SIRs among participants with gastroesophageal reflux disease and those using proton pump inhibitors (often for gastroesophageal reflux disease) were expected considering the strong and well-established association with esophageal adenocarcinoma.[13]

Additional large studies with long follow-up are required to confirm the results of this first study with sufficient statistical power and length of follow-up to provide conclusive results on the topic. Nevertheless, the findings of the study do suggest that eradication treatment for *H pylori* is safe from an esophageal cancer perspective. This is valuable knowledge when considering eradication treatment for individual patients and eradication programs in high-risk populations of gastric cancer. The results should be generalizable to other high-income countries with low prevalence of *H pylori* and high incidence of esophageal adenocarcinoma, but studies from other regions with different patterns of these conditions are warranted.

In conclusion, this multinational and population-based cohort study with long and complete follow-up found no increased risk of esophageal adenocarcinoma after *H pylori* eradication treatment. These results indicate that *H pylori* eradication treatment is safe from a cancer perspective and that it will not increase the incidence of this tumor. This is valuable knowledge when considering *H pylori* eradication treatment of individual patients as well as entire populations.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.03.016.

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The authors disclose no conflicts.

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Data Availability
The data will not be made available for other researchers because of legal restrictions.

Supplementary Table 1. ICD Codes and Versions Used to Define Adenocarcinoma of the Esophagus and the Gastroesophageal Junction, as Well as Squamous Cell Carcinoma of the Esophagus, as Identified in the Nordic Cancer Registers

	Topography code[a]			Histology code[b]		Behavioral code[c]
	ICD-7	ICD-9	ICD-10	ICD-03	C24	ICD-03
Esophageal adenocarcinoma	150	150	C15	8140-8149, 8160-8162, 8190-8221, 8260-8337, 8350-8551, 8570-8576, 8940-8941	096	3 = malignant tumor
Gastroesophageal junction adenocarcinoma	151.1	151.0	C16.0			
Esophageal squamous cell carcinoma	150	150	C15	8051-8084, 8120-8131	146	

ICD, International Statistical Classification of Disease and Related Health Problems; ICD-O, International Classification of Diseases for Oncology.
[a]ICD code version 7, 9, or 10.
[b]ICD-O code version 3 (first 4 digits), or C24 histology code.
[c]ICD-O code version 3 (5th digit).

Supplementary Table 2. ICD Codes and Versions Used to Identify Gastroesophageal Reflux and Included Conditions, by Country

	Sweden	Finland	Denmark	Iceland	Norway
Gastroesophageal reflux disease	ICD-10: K21.9	ICD-10: K21.9	ICD-10: DK21.9	ICD-10: K21.9	ICD-10: K21.9
Hiatal hernia	ICD-7: 560.40 ICD-8: 551.30 ICD-9: 553D ICD-10: K44	ICD-7: 560.40 ICD-8: 551.30 ICD-9: 5513A ICD-10: K44	ICD-8: 551.30, 551.39 ICD-10: DK44	ICD-10: K44	ICD-10: K44
Heartburn	ICD-7: 784.30 ICD-8: 784.30 ICD-9: 787B ICD-10: R12	ICD-7: 784.30 ICD-8: 784.30 ICD-9: 7871A ICD-10: R12	ICD-8: 784.39 ICD-10: DR12	ICD-10: R12	ICD-10: R12
Esophagitis	ICD-7: 539.11, 539.12 ICD-8: 530.93, 530.94 ICD-9: 530B, 530C ICD-10: K20, K21.0	ICD-7: 539.11, 539.12 ICD-8: 530.93, 530.94 ICD-9: 5301A, 5301C-D, 5301X ICD-10: K20, K21.0	ICD-8: 530.90 ICD-10: DK20, DK21.0	ICD-10: K20, K21.0	ICD-10: K20, K21.0
Barrett's esophagus	ICD-10: K22.7	ICD-9: 5301B ICD-10: K22.7	ICD-10: DK22.7	ICD-10: K22.7	ICD-10: K22.7

Abbreviations as in Supplementary Table 1.

Supplementary Table 3. The Anatomical Therapeutic Chemical Codes Used to Identify Long-Term Medication With Proton Pump Inhibitors, Nonsteroidal Anti-Inflammatory Drugs, and Statins, in the Nordic Prescribed Drug Registers

	Proton pump inhibitors	Nonsteroidal anti-inflammatory drugs	Statins
Anatomical Therapeutic Chemical codes	A02BC	M01A, N02BA, B01AC06, C10BX01, C10BX02, C10BX04, C10BX05, C10BX06, C10BX08, C10BX12, C07FX02, C07FX03, C07FX04	C10AA, C10B

Supplementary Table 4. Sensitivity Analyses Excluding Reinfected Patients (>12, 12–24, and 12–36 mo) After *H pylori* Eradication Treatment, Presenting Risk of Esophageal Adenocarcinoma After Eradication Treatment in the Nordic Countries

Exclusion	Study cohort after exclusions	SIR (95% CI), y after baseline			
		0–23 y (total)	0–4 y	5–9 y	10–23 y
All with reinfection >12 mo after treatment[a]	615,534	0.87 (0.80–0.95)	1.11 (0.97–1.26)	0.77 (0.65–0.90)	0.71 (0.59–0.85)
Reinfection 12–24 mo after treatment[b]	601,016	0.84 (0.77–0.93)	1.01 (0.88–1.17)	0.76 (0.64–0.89)	0.72 (0.59–0.87)
Reinfection 12–36 mo after treatment[c]	549,473	0.83 (0.75–0.91)	1.00 (0.87–1.16)	0.71 (0.59–0.84)	0.73 (0.58–0.90)

NOTE. Baseline (start of follow-up) set to.
[a]12 months
[b]24 months
[c]36 mo after *H pylori* eradication treatment.

Supplementary Table 5. Sensitivity Analyses Excluding Gastroesophageal Junction Adenocarcinoma, Presenting Risk of Esophageal Adenocarcinoma After *H pylori* Eradication Treatment in the Nordic Countries

	Esophageal adenocarcinoma, excluding adenocarcinoma of the gastroesophageal junction	
	Observed vs expected no. of cases	SIR (95% CI)
Entire follow-up	274 vs 319	0.86 (0.76–0.97)
Sex		
Male	214 vs 254	0.84 (0.73–0.96)
Female	60 vs 65	0.93 (0.71–1.19)
Years after eradication treatment		
1–5	113 vs 112	1.01 (0.83–1.22)
6–10	90 vs 110	0.73 (0.57–0.92)
11–24	71 vs 97	0.73 (0.57–0.92)