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Risk of Gastric Adenocarcinoma After Eradication of *Helicobacter pylori*

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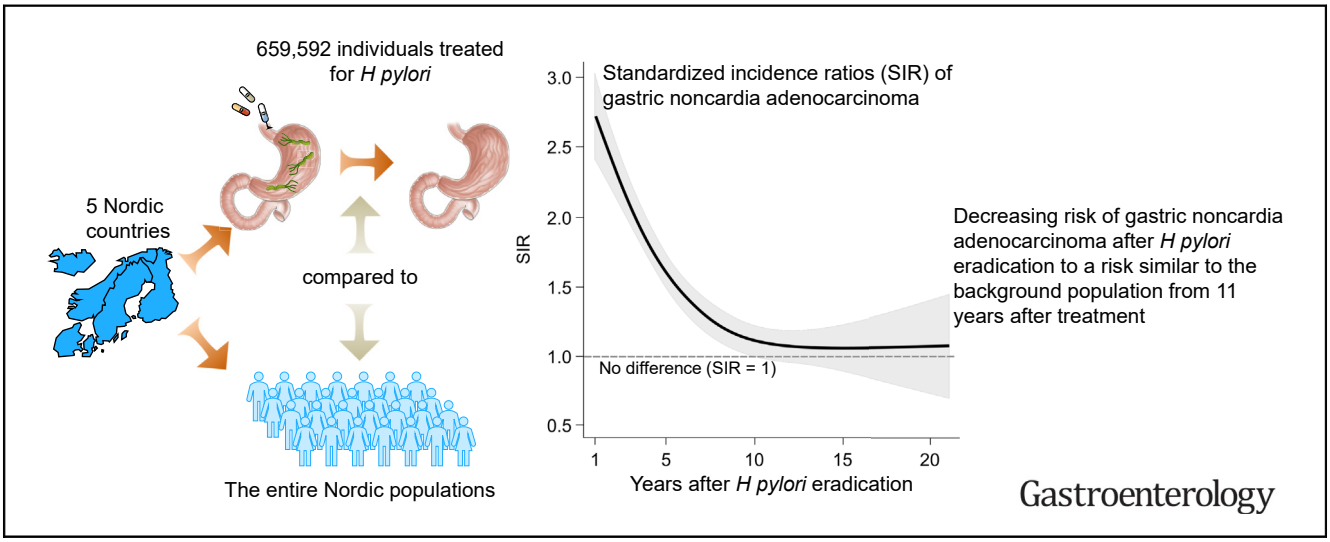

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BACKGROUND & AIMS: *Helicobacter pylori* infection of the stomach is the main risk factor for gastric noncardia adenocarcinoma; however, less is known on how eradication of *H pylori* influences the risk of this tumor over time, particularly in Western populations. The aim of this study was to delineate how the risk of gastric noncardia adenocarcinoma develops over time after *H pylori* eradication treatment in a Western population compared with the background population. **METHODS:** This population-based cohort study included all adults having received *H pylori* eradication treatment between 1995 and 2019 in any of the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) were calculated by comparing the gastric noncardia adenocarcinoma incidence in the study cohort with the incidence in the background population of the same age, sex, calendar period, and country. Time trends in SIR were assessed using Poisson regression. **RESULTS:** Among 659,592 participants having received *H pylori* eradication treatment, contributing 5,480,873 person-years at risk, 1311 developed gastric noncardia adenocarcinoma. During up to 24 years of follow-up, the SIR was initially higher than the background population (SIR, 2.27; 95% CI 2.10–2.44, 1–5 years after treatment), and then gradually decreased over time and approached the level of the background population from 11 years after treatment (SIR, 1.11; 95% CI 0.98–1.27, 11–24 years after treatment). **CONCLUSION:** This study revealed a decreasing incidence of gastric noncardia adenocarcinoma after *H pylori* eradication treatment in 5 Western populations. The risk became virtually similar to the background population from 11 years after treatment.

Keywords: Helicobacter pylori Eradication; Gastric Neoplasm; Gastric Cancer; Cohort Study; Multinational; Population-Based.

Infection of the stomach with *Helicobacter pylori* is the most prevalent bacterial infection worldwide, found in approximately 50% of the global population, but with striking geographical variations in prevalence and virulence.[1] The highest prevalence (>80%) and virulence are found in countries with low socioeconomic status and sanitation standards (ie, regions in Africa and Western Asia). In high-income areas, including the Nordic countries in Europe, the prevalence is <30% and also the virulence is lower.[2] Although most infected individuals are asymptomatic, many will sooner or later develop chronic inflammation of the gastric mucosa and peptic ulcer disease.[3] *H pylori* infection is strongly and causally associated with gastric noncardia adenocarcinoma, and 1% of infected individuals will develop gastric adenocarcinoma during their lifetime.[4–8] Gastric adenocarcinoma is the fourth most common cause of cancer-related death globally, causing 660,000 deaths in 2022.[9] In most areas worldwide, the geographical variation in gastric adenocarcinoma mirrors the population prevalence of *H pylori*, and the steady decline in gastric adenocarcinoma in high-income countries is mainly explained by a declining prevalence of this bacterium.[6,10]

Systematic reviews have reported that *H pylori* eradication treatment reduces the incidence of gastric adenocarcinoma by 50% in high-prevalence areas such as Asia.[11–13] But little is known about whether and to what extent eradication treatment decreases the risk of gastric adenocarcinoma in Western populations, where the demography, *H pylori* prevalence and virulence, and etiology of gastric adenocarcinoma are vastly different.[14–16] It is also unknown if and how long it takes until the cancer risk equals that of the general population after eradication.

The aim of this study was to delineate how the risk of gastric noncardia adenocarcinoma develops over time after *H pylori* eradication treatment in a Western population.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Helicobacter pylori infection is the main risk factor for gastric adenocarcinoma. Less is known on how eradication of *Helicobacter pylori* influences the risk of this tumor, particularly in Western populations.

NEW FINDINGS

The risk of gastric noncardia adenocarcinoma decreased after eradication treatment of *Helicobacter pylori* in 5 Western countries and became similar to the background population from 11 years after treatment.

LIMITATIONS

Residual confounding cannot be excluded in this observational study.

CLINICAL RESEARCH RELEVANCE

Helicobacter pylori eradication treatment may be used in the prevention of gastric noncardia adenocarcinoma in high-risk individuals.

BASIC RESEARCH RELEVANCE

Research is needed to delineate high-risk individuals of gastric noncardia adenocarcinoma, where screening for and eradication of *Helicobacter pylori* infection may be recommended.

Methods

Design

This was a population-based cohort study conducted in the 5 Nordic countries, that is, Denmark, Finland, Iceland, Norway, and Sweden (in alphabetical order). The incidence of gastric noncardia adenocarcinoma after eradication treatment of *H pylori* (exposed cohort) was compared with the incidence of this tumor in the corresponding background populations of the 5 countries. The total study period spanned from 1995 to the end of 2019, but the start year varied between the countries (1995 for Denmark and Finland, 2003 for Iceland, 2004 for Norway, and 2005 for Sweden). The study cohort was the "Nordic Helicobacter Pylori Eradication Project (NordHePEP)," which has been described in detail elsewhere.[17] In brief, NordHePEP includes all adult individuals (≥18 years) having been prescribed *H pylori* eradication treatment in any of the 5 Nordic countries. Information about prescribed drugs, cancer, medical diagnoses, surgical procedures, and mortality was retrieved from multiple national health data registries. The personal identity number that was given to each resident of the Nordic countries allowed all the data gathered about each study participant to be linked together. Ethical approvals and legitimate permissions were obtained from the relevant authorities within each country.[17]

Exposure

The exposure was eradication treatment of *H pylori*, consisting of a minimum 1-week regimen with 2 of the 3 antibiotics amoxicillin, clarithromycin, or metronidazole, in combination with a proton pump inhibitor. This is the recommended regimen in the Nordic countries, where it accomplishes successful eradication in 90% of infected individuals.[18–20] This regimen is also recommended for remaining infection after a first treatment attempt in these countries. The treatment requires a physician's prescription, which is automatically transferred to the national drug registries. The eradication treatment was regarded as unsuccessful if a repeated treatment was used by the same individual within 12 months of a previous treatment. Patients with less than 12 months of follow-up after eradication treatment were excluded. Thus, the exposure period ended in 2018.

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

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Outcome

The outcome was a diagnosis of gastric noncardia adenocarcinoma. Information regarding the incidence of gastric noncardia adenocarcinoma was retrieved from the national cancer registries, which have 98% complete recording of this tumor.[21,22] We excluded patients with a history of gastric cancer (regardless of histology) and those who developed gastric cancer less than 12 months after eradication treatment.

Statistical Analysis

The risk of noncardia adenocarcinoma was estimated by calculating standardized incidence ratios (SIRs), a method that requires complete coverage of all individuals in that of the background population in the country to be followed in the relevant national health data registries. This method allows for assessments of how the cancer risk in *H pylori*–eradicated individuals compares with that of the background populations. SIRs with 95% confidence intervals (CIs) were calculated by dividing the observed number of gastric noncardia adenocarcinoma cases in the *H pylori* eradication treatment cohort (NordHePEP) by the expected number of cases. The expected numbers were derived from the entire Nordic populations of the same age groups (5-year categories), sex (men and women), calendar period (1995–1999, 2000–2004, 2005–2009, 2010–2014, and 2015–2019), and country (Denmark, Finland, Iceland, Norway, and Sweden) as for the eradication treatment cohort. The follow-up started 1 year after eradication treatment and lasted until the occurrence of gastric cancer, death, emigration, or end of study period (December 31, 2019), whichever occurred first. Three follow-up periods were analyzed separately: 1–5, 6–10, and 11–24 years after eradication treatment. Continuous time trends were analyzed by means of Poisson regression with robust estimation of the variance, using the number of events as the outcome, cubic splines of time with 3 knots as the covariate, and the 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 CIs were estimated using a sandwich estimator of the variance.

Stratified analyses were performed for subgroups of sex (male and female), age ($\leq$55 years and >55 years), years after eradication treatment (presented previously), education level ($\leq$9 years or >9 years, retrieved from the education registries in Denmark and Sweden), comorbidity (Charlson comorbidity index[23] 0, 1, or $\geq$2 for comorbidities registered in the national patient registries within 5 years before eradication treatment), long-term proton pump inhibitor medication,[24] and long-term medication with a nonsteroidal anti-inflammatory drug.[25] Long-term medication was defined as a prescription of >180 tablets during the last 12 months before eradication treatment. This time window was used to avoid immortal time bias and the definition of >180 tablets was used to avoid including temporary use. In a sensitivity analysis, we censored patients who developed another histological type of gastric malignancy than adenocarcinoma during the follow-up.

Two experienced biostatisticians (G.S. and J.Y.) were responsible for the extensive data management as well as the statistical analyses. The statistical analyses followed a predefined study protocol, using Stata 16.1/17.0.

Results

Participants

The study included 659,592 patients having received *H pylori* eradication treatment, contributing to 5,480,873 person-years at risk during up to 24 years of follow-up (mean 8.3 years). Most were woman (54.3%), aged $\leq$50 years (61.5%), and without serious comorbidity (73.4% had Charlson comorbidity index 0) (Table 1). Characteristics of the patients with gastric adenocarcinoma in the study

Table 1. Characteristics of Cohort Participants Having Received Eradication Treatment of *Helicobacter pylori*

Characteristic	Number (% of total cohort)
Total cohort	659,592 (100.0)
Sex	
Men	301,157 (45.7)
Women	358,435 (54.3)
Age (*y*)	
18–30	59,165 (9.0)
31–40	82,534 (12.5)
41–50	112,441 (17.0)
51–60	138,266 (21.0)
61–70	133,468 (20.2)
71–80	96,167 (14.6)
>80	37,551 (5.7)
Country	
Denmark	145,462 (22.1)
Finland	265,622 (40.3)
Iceland	8,017 (1.2)
Norway	58,425 (8.9)
Sweden	182,066 (27.6)
Calendar year period	
1995–1999	48,057 (7.3)
2000–2004	124,734 (18.9)
2005–2009	185,886 (28.2)
2010–2014	176,645 (26.8)
2015–2018	124,270 (18.8)
Education (data only available for Denmark and Sweden)	
$\leq$9 years	109,821 (33.5)
>9 years	191,534 (58.5)
Missing	26,173 (8.0)
Charlson comorbidity index[a]	
0	483,928 (73.4)
1	99,826 (15.1)
$\geq$2	45,029 (6.8)
Missing	30,809 (4.7)
Long-term medication[b]	
Proton pump inhibitors	70,261 (10.7)
Nonsteroidal anti-inflammatory drugs	79,270 (12.0)

[a]Recorded in a patient registry within 5 years before eradication treatment of *H pylori*.
[b]More than 180 tablets prescribed within 1 year before eradication treatment of *H pylori*.

cohort compared with those in the background population showed only minor differences (Supplementary Table 1).

Risk of Gastric Adenocarcinoma

A total of 1311 patients developed gastric noncardia adenocarcinoma during follow-up of the cohort having received *H pylori* eradication treatment, compared with 800 expected in the corresponding background population. This resulted in an overall SIR of 1.64 (95% CI, 1.55–1.73). The overall SIR was similar in men and women, but higher in younger compared with older participants (Table 2). The SIR for all cohort participants was initially higher than the background population (SIR, 2.27; 95% CI, 2.10–2.44, 1–5 years after eradication), but decreased over time and approached the level of the background population after 11 to 24 years of follow-up (SIR, 1.11; 95% CI, 0.98–1.27) (Table 2). The continuous time trend analysis using Poisson regression revealed gradually a declining SIR during the first 1 to 10 years of follow-up after eradication treatment, after which the SIR plateaued at a level just above 1 from 11 years onward (Figure 1).

The SIR decreased with longer follow-up time also in all subgroups of sex, age, education level, comorbidity scores, and long-term medication with a proton pump inhibitor or nonsteroidal anti-inflammatory drug, but the SIRs were seemingly higher in women than in men and in younger participants compared with older (Table 3).

The sensitivity analysis censoring patients with gastric malignancies other than noncardia adenocarcinoma after eradication treatment confirmed the results in the main analyses, that is, decreasing SIRs over time after *H pylori* eradication treatment, and without any statistically significantly increased SIR remaining 11 to 24 years after eradication treatment of *H pylori* (Table 4).

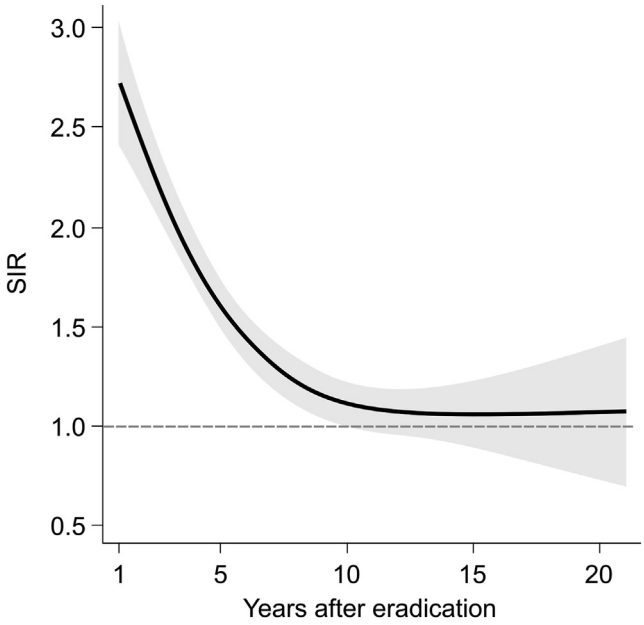

Figure 1. Risk of gastric noncardia adenocarcinoma after eradication treatment of *Helicobacter pylori* (x-axis) compared with the corresponding general populations of the 5 Nordic countries, presented as SIRs (y-axis) with 95% CIs (*shaded area*) using Poisson regression with robust variance estimation and cubic splines of time with 3 knots.

Discussion

This study from 5 Western countries indicates a decreasing risk of gastric noncardia adenocarcinoma over time after eradication treatment of *H pylori* infection, and suggests the risk was virtually similar to that of the background population from 11 years after the treatment.

Table 2. Risk of Gastric Noncardia Adenocarcinoma After Eradication Treatment of *Helicobacter pylori* Compared With the Corresponding Background Nordic Populations

	Gastric noncardia adenocarcinoma	
	Observed vs expected number of cases	Standardized incidence ratio (95% CI)
Total	1311 vs 800	1.64 (1.55–1.73)
Years after eradication treatment		
1–5	702 vs 310	2.27 (2.10–2.44)
6–10	374 vs 279	1.34 (1.21–1.48)
11–24	235 vs 211	1.11 (0.98–1.27)

Strengths of the study include the multinational and population-based design with close to complete inclusion of all individuals having received *H pylori* eradication treatment, as well as the long and complete follow-up. The Nordic health data registries have nationwide coverage and the variables are of high validity, which is a requirement for calculating SIRs and thus make direct comparisons with the corresponding background population. The personal identity number systems in all Nordic countries enabled individual-level linkage of medical data.[17] Among limitations is the possible misclassification of *H pylori* eradication treatment. Some participants may not have completed the eradication treatment; however, we expect compliance to be high because the exposure definition required a prescription from a physician together with a manual dispensation and payment by the patient. Antibiotic resistance can lead to treatment failure,[26] but *H pylori* triple treatment resistance is low in Northern Europe and the treatment accomplishes an eradication rate of approximately 90%.[27] The study lacks information on *H pylori* eradication success, but national clinical guidelines recommend a control test and retreatment if eradication is not achieved. Nevertheless, misclassification of *H pylori* eradication treatment would not explain the decreasing risk of gastric noncardia adenocarcinoma over time after *H pylori* treatment but would rather dilute this risk reduction. The control group was the corresponding population of each entire country, and it was not possible to remove those who had received *H pylori* eradication treatment from the populations. Thus, the 659,592 patients who received *H pylori* treatment in the study cohort were also included in the background population used for

Table 3. Risk of Gastric Noncardia Adenocarcinoma After Eradication Treatment of *Helicobacter pylori* Compared With the Background Populations of the 5 Nordic Countries, Stratified by Education, Comorbidity, and Long-Term Medications

	SIR (95% CI), years after eradication treatment			
	1–24 years (all)	1–5 years	6–10 years	11–24 years
Sex				
Men	1.54 (1.42–1.66)	2.12 (1.91–2.35)	1.31 (1.13–1.50)	0.98 (0.83–1.18)
Women	1.75 (1.62–1.89)	2.44 (2.19–2.71)	1.38 (1.18–1.60)	1.26 (1.05–1.51)
Age at entry, *y*				
≤55	2.53 (2.27–2.80)	4.73 (4.01–5.49)	2.19 (1.78–2.65)	1.46 (1.17–1.80)
>55	1.45 (1.35–1.54)	1.94 (1.78–2.11)	1.17 (1.03–1.32)	0.98 (0.83–1.15)
Education, *y*[a] (data only available for Denmark and Sweden)				
≤9	2.00 (1.73–2.30)	2.81 (2.33–3.37)	1.53 (1.15–2.01)	1.20 (0.80–1.75)
>9	2.03 (1.80–2.30)	3.01 (2.58–3.55)	1.53 (1.19–1.95)	1.09 (0.76–1.52)
Charlson comorbidity index[b]				
0	1.63 (1.55–1.76)	2.49 (2.27–2.72)	1.28 (1.13–1.45)	1.10 (0.95–1.27)
1	1.52 (1.32–1.73)	1.79 (1.48–2.14)	1.36 (1.06–1.71)	1.21 (0.86–1.67)
≥2	1.84 (1.51–2.23)	1.88 (1.44–2.41)	1.96 (1.37–2.72)	1.33 (0.60–2.51)
Long-term medication[c]				
Proton pump inhibitors				
Yes	2.05 (1.69–2.46)	2.54 (2.00–3.18)	1.43 (0.95–2.06)	1.76 (0.94–3.01)
No	1.61 (1.52–1.70)	2.24 (2.06–2.42)	1.33 (1.20–1.48)	1.09 (0.95–1.24)
Nonsteroidal anti-inflammatory drugs				
Yes	1.31 (1.10–1.54)	1.46 (1.15–1.83)	1.16 (0.85–1.56)	1.15 (0.70–1.80)
No	1.69 (1.60–1.79)	2.43 (2.24–2.63)	1.37 (1.23–1.52)	1.11 (0.97–1.27)

[a]Recorded in the population registry at time of eradication, data only available for Denmark and Sweden.
[b]Recorded in a patient registry within 5 years before eradication treatment of *H pylori*.
[c]More than 180 tablets prescribed within 1 year before eradication treatment of *H pylori*.

comparison. However, the patients who received such treatment constitute only a small part (3%) of the total adult population (approximately 22 million adults). Therefore, any dilution of associations would be negligible. To avoid biased estimates due to the differences in calendar periods and use of eradication treatment between the countries, the comparison cohort of the general population was matched for both calendar year and country to mimic the distribution of the cohort receiving *H pylori* treatment. Tumor misclassification of cardia and noncardia gastric adenocarcinoma is possible.[28] However, a comprehensive validation study of the Swedish Cancer Registry found only 2% of recorded noncardia adenocarcinomas being misclassified as cardia adenocarcinomas.[21] In addition, tumor misclassification cannot explain the decreasing risk estimates with longer follow-up after eradication treatment. Although confounding cannot be excluded, it is not plausible that confounding would explain the pattern of gradually decreasing risk estimates with longer follow-up after eradication treatment. The possibility that the increased risk of gastric adenocarcinoma during the initial period after eradication is explained by detection bias (ie, that individuals are at higher risk of gastric cancer closer to the *H pylori* test), seems unlikely because the results show that it takes 11 years to reach the level of the background population, and any detection bias should be evident only during the initial year. The increased SIRs initially after eradication treatment were expected due to the link between *H pylori* infection and gastric noncardia adenocarcinoma.

The stratified analyses of all subgroups of sex, age, education, comorbidity, proton pump inhibitor medication, and use of nonsteroidal anti-inflammatory drugs showed decreasing risk estimates of developing gastric noncardia adenocarcinoma over time after eradication treatment of *H pylori* infection. This consistency provides support for the overall result. The seemingly higher risk estimates in younger participants are not supported by the evidence showing that *H pylori* eradication is more effective in younger individuals

Table 4. Sensitivity Analyses, Presented as the Risk of Gastric Noncardia Adenocarcinoma After *Helicobacter pylori* Eradication Treatment in the Nordic Countries After Censoring Patients From the Date of a Diagnosis of Any Other Gastric Malignancies Than Noncardia Adenocarcinoma

SIR (95% CI)			
1–24 years (all)	1–5 years	6–10 years	11–24 years
1.64 (1.55–1.73)	2.27 (2.10–2.44)	1.34 (1.21–1.48)	1.12 (0.98–1.27)

before the onset of precursor lesions.[29] A more plausible explanation may be that younger patients with symptoms are more likely to develop cancer than older symptomatic patients, or that the finding is merely due to chance. Chance might also explain the potential sex difference in association. The study showed an SIR of 1.11 (95% CI, 0.98–1.27) in the 11 to 24 years of follow-up after treatment of *H pylori*, which is still >1. However, the estimate was statistically nonsignificant despite good statistical power, the Poisson regression analysis showed stable point estimates close to 1 throughout the follow-up between 11 and 24 years after eradication treatment, and a relative risk difference of developing gastric adenocarcinoma of 11% is less clinically relevant because of the low incidence of this tumor.

The association between *H pylori* infection and gastric noncardia adenocarcinoma is well established.[30] Carcinogenesis is triggered by *H pylori*–induced gastritis that progresses into mucosal atrophy, intestinal metaplasia, and dysplasia, and finally into invasive adenocarcinoma.[31] Previous studies have suggested that eradication of *H pylori* may prevent progression of manifest intestinal metaplasia, and even regress intestinal-type precancerous lesions in the gastric mucosa.[32,33] However, studies with longer follow-up have reported contradictory results regarding the influence of eradication and long-term gastric cancer risk.[29,34–36]

The results of this study from 5 entire Western countries are in line with systematic reviews from Asian populations, indicating that *H pylori* eradication reduces the risk of gastric cancer.[13] However, other studies have not been able to assess whether and when the risk returns to that of the background population. In addition, it has been proposed that eradication of *H pylori* might increase the risk of esophageal adenocarcinoma, but our recent study based on the NordHePEP found no such increase.[37] When considered collectively, it may be beneficial and safe to recommend *H pylori* eradication treatment in the prevention of gastric noncardia adenocarcinoma. Research is needed to better delineate people at high risk of this tumor where screening for *H pylori* and eradication of this infection may be both cost-effective and beneficial for society and individuals.

In conclusion, this large and population-based cohort study from the 5 Nordic countries, with long and complete follow-up, suggests that eradication treatment of *H pylori* gradually and substantially decreases the risk of gastric noncardia adenocarcinoma in Western countries and that the risk became almost similar to the background population from 11 years after treatment.

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.2025.01.239.

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Conflicts of interest
The authors disclose no conflicts.

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Data Availablity
The data used in this study are available from Statistics Denmark, but restrictions apply to the availability of these data, which were used under license, and thus not publicly available. It is recommended to contact the corresponding author for further information.

Supplementary Table 1. Characteristics of Patients With Gastric Adenocarcinoma in the Study Cohort of Individuals Having Received Eradication Treatment for *Helicobacter pylori* and in the Comparison Cohort of Individuals in the Corresponding Background Population

Characteristic	Gastric adenocarcinoma patients in the *Helicobacter pylori* eradication cohort, n (%)	Gastric adenocarcinoma patients in the background population, n (%)
Total	1,311 (100.0)	30,953 (100.0)
Sex		
Men	663 (50.6)	16,978 (54.6)
Women	648 (49.4)	13,975 (45.1)
Age (*y*)		
18–30	9 (0.7)	115 (0.4)
31–40	57 (4.4)	455 (1.5)
41–50	159 (12.1)	1,533 (5.0)
51–60	297 (22.7)	3,681 (11.9)
61–70	368 (29.6)	6,931 (22.4)
71–80	315 (24.0)	9,576 (30.9)
>80	86 (6.6)	8,662 (28.0)
Country		
Denmark	235 (17.9)	6,547 (21.2)
Finland	744 (56.8)	12,394 (40.0)
Iceland	14 (1.1)	501 (1.6)
Norway	75 (5.7)	4,278 (13.8)
Sweden	243 (18.5)	7,233 (23.4)
Calendar year		
1995–1999	174 (13.3)	4,845 (15.6)
2000–2004	384 (29.3)	4,333 (14.0)
2005–2009	433 (33.0)	8,313 (26.9)
2010–2014	254 (19.4)	7,795 (25.2)
2015–2018	66 (5.0)	5,667 (18.3)