HHS Public Access

Author manuscript

Aliment Pharmacol Ther. Author manuscript; available in PMC 2021 April 23.

Published in final edited form as:

Aliment Pharmacol Ther. 2020 April ; 51(8): 781–788. doi:10.1111/apt.15677.

Oesophageal and proximal gastric adenocarcinomas are rare after detection of *Helicobacter pylori* infection

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Summary

Background: *Helicobacter pylori* infection is the most important risk factor for non-proximal gastric adenocarcinoma, yet some posit it is protective against oesophageal adenocarcinoma and proximal gastric cancers.

Aims: To evaluate the incidence of and risk factors for future oesophageal and proximal gastric cancers, utilizing the largest North American cohort of patients with previously identified *H pylori*. Also to identify whether treatment and eradication of *H pylori* alter future oesophageal and proximal gastric cancer risk.

Methods: Retrospective cohort study within the Veterans Administration of 36 803 patients (median age 60.4 years; 91.8% male) with confirmed *H pylori* between 01 January 1994 and 31 December 2018. Primary outcome was diagnosis of future oesophageal and proximal gastric cancers. A time to event with competing risk analysis was performed, evaluating patient factors and whether the patient received *H pylori* treatment. Secondary analysis of those treated evaluated whether confirmed eradication was associated with cancer.

Results: The cumulative incidence of oesophageal and proximal gastric cancers 5, 10 and 15 years after *H pylori* detection was 0.145%, 0.26% and 0.34%. Risk of future oesophageal or proximal gastric cancer was similar amongst whites (reference), African Americans (SHR 0.87, 95%CI 0.57-1.43) and American Indians (SHR 1.31, 95%CI 0.18-9.60) but substantially reduced

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Author contributions: Shria Kumar, MD: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis. David C. Metz, MBBCh: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; study supervision. Gregory G. Ginsberg, MD: critical revision of the manuscript for important intellectual content. David E. Kaplan, MD, MSc: study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis; study supervision. David S. Goldberg, MD, MSCE: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; study supervision. All authors approved the final version of this article.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

in those of Asian (no cases amongst 213 H pylori positive) or native Hawaiian origin (no cases amongst 295 H pylori positive) ($P < .001$). Increasing age (SHR 1.17 per 5 years, 95% CI: 1.09-1.25, $P < 0.001$) and smoking (SHR 2.06, 95% CI: 1.33-3.18, $P = 0.001$) were associated with oesophageal and proximal gastric cancers. Neither treatment of *H pylori* nor eradication status were associated with cancer ($P > 0.20$).

Conclusions: In the largest study of US patients with *H pylori*, we demonstrate that rates of oesophageal and proximal gastric cancers after treatment of *H pylori* are low. Older age, and smoking are associated with future cancer, whilst Asian or Native Hawaiian race are protective. *H pylori* treatment and eradication are not associated with future cancer.

1 | INTRODUCTION

Helicobacter pylori is an established risk factor for non-cardia gastric cancers, with the World Health Organization labelling it a class 1 carcinogen.[1-3] Consensus guidelines within the US recommend eradication of *H pylori* when detected, using a multi-drug antibiotic regimen and subsequent re-testing for confirmation of eradication.[4] In countries with high prevalence of both *H pylori* and gastric cancer, such as Japan, *H pylori* eradication is a public health initiative, in order to decrease cancer-related mortality.[5-7] Yet despite its class 1 carcinogenic status, mass eradication of *H pylori* is not without controversy. Those who argue against mass eradication of *H pylori* point out a number of factors: antibiotic resistance, antibiotic associated diseases, and the risk of oesophageal and proximal (cardia) adenocarcinomas.[8-14]

There have been a number of studies investigating the inverse relationship between oesophageal adenocarcinoma and proximal stomach adenocarcinoma, both in the US, other Western countries, and Eastern countries such as Japan and China (where the incidence of oesophageal adenocarcinoma is lower).[8,10,11] The predominant hypothesis is that with improved sanitation conditions, there has been a decrease in *H pylori* prevalence during the past century, particularly in Western countries: this change in microbiota has paralleled lower rates of non-cardia cancer and higher rates of cardia cancer.[8,15] However, the evidence for this inverse relationship is not uniformly agreed upon, and therefore *H pylori's* importance in oesophageal and proximal gastric cancers remains unclear.[16-18] This controversy also poses a dilemma for the management of *H pylori* treatment, and whether eradication of *H pylori* should be reconsidered in particular groups.

To address this knowledge gap, we sought to determine the relationship between *H pylori* and subsequent oesophageal and proximal gastric cancers in order to help guide nuanced *H pylori* treatment, to maximise benefit while minimizing harm. We evaluate the incidence of and risk factors for future oesophageal and proximal gastric cancers, utilizing the largest North American cohort of patients with previously identified *H pylori*.[19] We also identify whether treatment and eradication of *H pylori* alter future oesophageal and proximal gastric cancers risk.

2 | METHODS

This retrospective cohort study was conducted within the Veterans Health Administration Corporate Data Warehouse which includes data from the unified electronic medical record of all Veterans Health Administration facilities (i.e. hospitals and outpatient) since 01 October 1999.

2.1 | Study cohort

We identified patients with *H pylori* infection, and this cohort has been extensively described elsewhere.[19] Briefly, patients with *H pylori* infection were included based on: 1) endoscopic pathology by natural language processing, 2) positive stool antigen test or 3) positive urea breath test. For patients with multiple criteria, the criterion with the earliest date were used. (Unique identifiers assured no duplications.)

2.2 | Study outcomes

The outcomes included both oesophageal adenocarcinoma and proximal (cardia) gastric adenocarcinomas. Both were identified using the Veterans Affairs Central Cancer Registry and/or ICD 9/10 codes.[20] The Central Cancer Registry is a comprehensive, national database of cancers diagnosed and treated in the Veterans Health Administration since 1995. ICD9/10 codes were used and included for oesophageal: ICD 9 150.9, 150.2, 150.5 and ICD 10 C15.5, 15.8, and 15.9 and for cardia cancer: ICD 9 151.0 and ICD 10 C16.0. There is no administrative code delineating the histologic subtype of oesophageal cancers, but oesophageal adenocarcinomas are the most common subtype of oesophageal cancer, particularly distally.[21,22] The diagnosis of either cancer was minimum 30 days after *H pylori* diagnosis to ensure testing was for *H pylori*, not a malignancy workup. We filtered to include cardia adenocarcinomas and oesophageal adenocarcinomas.

2.3 | Statistical analysis

We performed a time to event analysis using competing risk models, with start time the date of *H pylori* diagnosis. Follow-up time ended at development of oesophageal and proximal gastric cancers, death prior to oesophageal and proximal gastric cancers, development of non-proximal gastric adenocarcinoma, or end of follow-up. Death was considered a competing risk to oesophageal and proximal gastric cancers as patients could die from another cause, precluding the development of oesophageal and proximal gastric cancers, and factors associated with mortality might also be associated with oesophageal and proximal gastric cancers. Similarly, if patients developed non-proximal gastric adenocarcinoma, any predisposing factors may also be associated with oesophageal and proximal gastric cancers. Among the entire *H pylori* cohort, we evaluated covariates shown to be associated with various subtypes of foregut cancer: age at *H pylori* diagnosis, gender, race, ethnicity, history of ever smoking (current or prior diagnostic code)[23] and zip code-level poverty at *H pylori* diagnosis. Zipcode-level poverty was based on 2010 census data, categorised based on percentage of people within a zipcode below the federal poverty line. We also included whether the patient received prescription for an eradication regimen for *H pylori* as a covariate. Receipt of *H pylori* treatment was defined as receiving a recommended antibiotic

regimen after *H pylori* diagnosis at the Veterans Health Administration using prescription filling data at any inpatient or outpatient Veterans Health Administration facility.[19]

A secondary analysis sought to evaluate the association between eradication status and oesophageal and proximal gastric cancers, given varying rates of re-testing and successful *H pylori* treatment.[4,24] This analysis was restricted to those who received treatment for *H pylori*. Eradication was based on having either a negative stool antigen, urea breath test, and/or pathology (gastric biopsy on endoscopy) upon repeat testing. Failed eradication was defined as a positive stool antigen, urea breath test and/or pathology, or a positive *H pylori* test after a prior negative test given that true re-infection is exceedingly rare. Patients without any eradication testing were considered as "unknown" eradication status. *H pylori* status on pathology was determined by repeat natural language processing, which has been described elsewhere.[19] We excluded patients who had eradication testing via endoscopy within 90 days of eventual cancer diagnosis, as this was possibly performed for alarm symptoms, versus eradication testing alone.

Stata/IC 15.1 was used to perform backward selection, with inclusion of all clinically significant sub-hazard ratios (SHRs), where $P < 0.10$. The Institutional Review Boards of the Corporal Michael J. Crescenz VA Medical Center and the University of Pennsylvania approved this study.

3 | RESULTS

We identified 36 803 patients who had *H pylori* identified by pathology, stool antigen, or urea breath test between 01 January 1994 and 31 December 2018. Median age of the cohort was 60.4 years; 91.8% were male. Of these, 108 (0.29%) developed oesophageal and proximal gastric cancers. Table 1 compares those patients who did and did not develop oesophageal and proximal gastric cancers. Those who had future oesophageal and proximal gastric cancers were older, 64.5 vs 61.6 years, $P < 0.001$ and more likely to be male, 97.2% vs 91.8%, $P = 0.04$. There were no significant differences in race, but patients with future oesophageal and proximal gastric cancers were more likely to be non-Hispanic/Latino (4.6% vs 11.3%, $P = 0.01$). They were more likely to have a history of smoking, 35.2% vs 25.5%, $P = 0.02$.

The cumulative incidence of oesophageal and proximal gastric cancers at 5, 10 and 15 years after detection of *H pylori* was 0.15%, 0.26% and 0.34%, respectively. When compared to the development of distal gastric adenocarcinomas in the same cohort (persons with detected *H pylori* infection), where the incidence of non-proximal gastric adenocarcinomas at 5, 10 and 20 years was 0.37%, 0.5% and 0.65%, respectively, the development of oesophageal and proximal gastric cancers is markedly lower, as seen in Figure 1.

We then evaluated for factors associated with future oesophageal and proximal gastric cancers using the multivariable competing risk time to event model (Table 2). Increasing age was associated with an increased risk of future oesophageal and proximal gastric cancers SHR: 1.17; 95% CI: 1.09-1.25, $P < 0.001$ (for each 5-year increase in age at time of *H pylori* detection). Black, Asian, and Native Hawaiian/Pacific Islanders were less likely to develop

future oesophageal and proximal gastric cancers as compared to white patients, $P < 0.001$, while patients with a history of smoking were more likely to develop future oesophageal and proximal gastric cancers, SHR: 2.06; 95% CI: 1.33-3.18, $P = 0.001$. Those of Hispanic or Latino ethnicity were less likely to develop future oesophageal and proximal gastric cancers compared to those of non-Hispanic or Latino ethnicity, 0.57 (0.22-1.46), $P = 0.06$. Figure 2 displays cumulative incidence curves. Importantly, in the multivariable model, whether the patient received prescription for an eradication regimen for *H pylori* was not found to be significant, and was not included in the final model.

A secondary analysis limited to those patients who were prescribed treatment for *H pylori* evaluated the association of *H pylori* eradication status with future oesophageal and proximal gastric cancers. Among the 27 748 patients who received a prescription for *H pylori* eradication, 8474 (30.5%) underwent subsequent re-testing. Of these 8474, 7541 (89.0%) had confirmed *H pylori* eradication and 933 (11.0%) had persistent *H pylori* infection. Of the 27 748 patients who received a prescription for *H pylori* eradication, eradication status was unknown in 19 274 (69.5%). During model building, eradication status was not significant and not included in the final model. Figure 3 displays the difference in future oesophageal and proximal gastric cancers by *H pylori* eradication status. As compared to those with persistent infection, there was no significant difference in future oesophageal and proximal gastric cancers among those with confirmed eradication of *H pylori* (SHR 3.28, 95% CI: 0.45-24.10) or unknown eradication status (SHR 2.29, 95% CI: 0.32-16.46). The difference between groups was not significant ($P = 0.22$) and as such, was not included in the final multivariable model. Results of the final multivariable analysis of this secondary analysis are displayed in Table S1. To note, among this same cohort, persons with both confirmed eradication and unknown eradication status had a markedly lower risk of future non-proximal gastric adenocarcinoma, versus those with persistent infection (SHR for those with confirmed eradication 0.24, 95% CI: 0.15-0.41 and for those with unknown eradication status 0.16, 95% CI: 0.10-0.25, $P < 0.001$).[19]

4 | CONCLUSIONS

In the largest cohort of US patients with confirmed *H pylori*, we demonstrate that rates of oesophageal and proximal gastric cancers after detection of *H pylori* are low: the cumulative incidence at 5, 10 and 15 years was 0.15%, 0.26% and 0.34%, respectively. Importantly, we found that *H pylori* treatment and eradication status were not associated with future oesophageal and proximal gastric cancers.

Our results can be loosely compared to future cancer incidence after identification of known risk factors and precursor lesions. For example, we previously conducted the largest study of gastric cancer among US patients with diagnosed *H pylori*, and demonstrated that the incidence of non-proximal gastric adenocarcinomas after *H pylori* diagnosis at 5, 10 and 20 years was 0.37%, 0.5% and 0.65%, respectively. Thus, the incidence of oesophageal and proximal gastric cancers after *H pylori* detection is markedly lower than non-proximal gastric cancer after *H pylori* detection. It is more difficult to compare oesophageal and proximal gastric cancers incidence after *H pylori* to baseline estimates. The American Cancer Society estimates a lifetime risk of oesophageal cancer in the United States is about

1 in 132 (0.76%) in men and about 1 in 455 (0.22%) in women.[25] Our study demonstrates that rates of oesophageal and proximal gastric cancers after treatment of *H pylori* are low, but may be so since our data does not capture a true lifetime estimate.

Most importantly, we demonstrate that treatment or eradication of *H pylori* is not associated with future oesophageal and proximal gastric cancers. As we note above, there are a large number of studies, both in Western and Eastern countries, that demonstrate an inverse relationship between oesophageal and proximal gastric cancers and *H pylori*.[8,10,11] Not all studies have demonstrated this, however, especially when accounting for virulence factors associated with *H pylori*.[17,26] This has led to differing opinions on the impact of *H pylori* detection and eradication, and whether we are truly eradicating a class 1 carcinogen, or in fact, unintentionally altering acid secretion and the human microbiome, or even potentially causing the rise of other malignancies. While guidelines have suggested there is no evidence that *H pylori* eradication alters acid secretion on its own, its role in the microbiome and in carcinogenesis of other cancers have not been fully defined.[27] Our study is the largest, to our knowledge, investigating the relationship between oesophageal and proximal gastric cancers and *H pylori*. It is further limited to US patients, which is important given the heterogeneous prevalence of *H pylori* among various countries, and the particularly concerning the rise of both oesophageal and proximal gastric cancers in the US.[28-30] These two factors make a US-based study such as ours critical to fill knowledge gaps. Since *H pylori* eradication's role in oesophageal and proximal gastric cancers remains controversial, our study provides a unique perspective in (a) identifying true *H pylori* infection (versus serology indicating previous exposure), (b) granular data, (c) prescription of treatment and (d) whether that treatment was truly effective in eradicating *H pylori*. We have previously demonstrated in the same cohort that *H pylori* eradication decreases future risk of non-proximal gastric adenocarcinomas. Here, we demonstrate that *H pylori* eradication does not impact the risk of future oesophageal and proximal gastric cancers.

Patients of older age were more likely to develop future oesophageal and proximal gastric cancers, and age is a known risk factor for all cancers.[31,32] Similarly, smokers were more likely to develop future oesophageal and proximal gastric cancers, consistent with previous literature.[33-35] Our findings regarding race and ethnicity are also similar to previously published studies. Those of Black, Asian, and Native Hawaiian/Pacific Islander were less likely to develop future oesophageal and proximal gastric cancers, as were those of Hispanic or Latino ethnicity, though this was not statistically significant. Asian Americans, Hispanics and African Americans, as well as immigrants and native populations, are known to have a disproportionate burden of gastric cancer in the US, particularly distal cancers.[36-39] Non-Hispanic whites, on the contrary, are more affected by oesophageal and proximal gastric cancers.[40-43] While these findings are not novel, they validate prior studies, and demonstrate how our cohort has risks consistent with other patient populations, and reinforce the external validity of our results.

There are several limitations to this study. First, its retrospective nature diminishes the ability to determine causality. Second, the cohort has some inherent selection bias (those tested for *H pylori* are being tested for some clinical reason), and we are unable to compare to it a confirmed background or control population without *H pylori*. Third, that we used the

Veterans Health Administration also limits the generalisability of the study somewhat, as it is a predominantly male (>90%) veteran population. However, our findings are consistent with known trends in oesophageal and proximal gastric cancers, as evidenced by our findings regarding age, smoking, race and ethnicity. This suggests external validity of our findings. This point is further underscored by our previously published study using the same cohort, identifying the incidence and risk factors for nonproximal gastric adenocarcinoma after *H pylori* detection.[19] In that study, we identified that compared to persistent *H pylori* infection, eradication of *H pylori* had a SHR of 0.24 (95% CI: 0.15-0.41, $P < 0.001$) for future non-proximal gastric adenocarcinoma. A recently published randomised control trial evaluating the impact of *H pylori* eradication among those at high risk of gastric cancer found a near-identical point estimate (HR 0.27; 95% CI: 0.10-0.70) when comparing the development of cancer in those who had persistent infection versus those who had confirmed eradication of *H pylori*.[44] This finding of real-world data providing a nearly identical point estimate for the decreased risk of gastric cancer after *H pylori* eradication provides strong evidence for the external validity of our cohort. Fourth, there are possibilities for false-negative/positive testing. Fifth, there could be measurement issues, leading to misclassification. These include patients receiving care outside the Veterans Health Administration, limiting available oncologic diagnoses and cancer registry inputs or *H pylori* diagnoses. However, misclassification of *H pylori* status would only affect inclusion into the cohort, and misclassification of the outcome, inadvertently including a distal gastric adenocarcinoma, would only bias toward the null since risk factors for distal and proximal cancer differ in terms of age, race and ethnicity.[45] For oesophageal cancers, administrative codes do not distinguish between adenocarcinoma and squamous cell, but are labelled anatomically. The majority of oesophageal adenocarcinomas are found distally, and the majority of squamous are proximal. Inadvertent inclusion of squamous oesophageal cancers would only increase the outcome incidence rate, which is already demonstrably low. Lastly, we were unable to determine eradication status for a number of patients. This may have underpowered our statistical analysis, and limited our ability to detect a difference, though in our previous study low re-testing rates did not limit power.[19]

The strengths of our study lie mainly in our robust cohort and ability to identify granular data with broad and longitudinal follow-up. Previous literature has focused on an association between *H pylori* and oesophageal and proximal gastric cancers, but this is the first study to identify the incidence of oesophageal and proximal gastric cancers after *H pylori* detection. We demonstrate that neither prescription of *H pylori* treatment nor eradication of *H pylori* are associated with future oesophageal and proximal gastric cancers. Given the previously demonstrated higher risk of distal gastric cancer after *H pylori*, benefits of *H pylori* treatment may outweigh the risk of future oesophageal and proximal gastric cancers in particular groups, including Blacks, Asians, and Native Hawaiians/Pacific Islanders. Future studies should continue to identify which cohorts would benefit most from *H pylori* screening and eradication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Declaration of personal interests: Shria Kumar, MD: Travel (Boston Scientific Corporation, Olympus Corporation). David C. Metz, MBBCh: Consulting (Takeda, Lexicon, AAA. Novartis), Grant Support (Lexicon, Wren Laboratories, Ipsen, AAA). Gregory G. Ginsberg, MD: Consulting (Boston Scientific Corporation), Consulting (Olympus Corporation). David E. Kaplan, MD, MSc: Research grant support (Gilead, Bayer). David S. Goldberg, MD, MSCE: Research grant support (Gilead, Merck, AbbVie, Zydus).

Funding information

Shria Kumar, MD is supported by an NIH training grant (5 T32 DK 7740-22).

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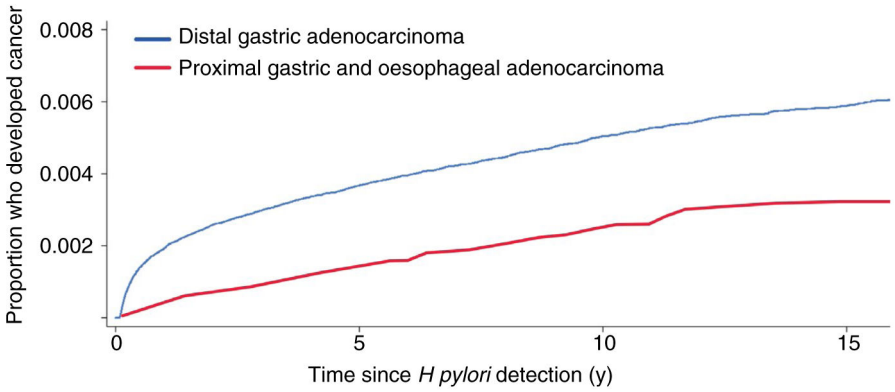

FIGURE 1.

The development of oesophageal and proximal gastric cancers versus the development of distal gastric adenocarcinomas after detection of *Helicobacter pylori infection*

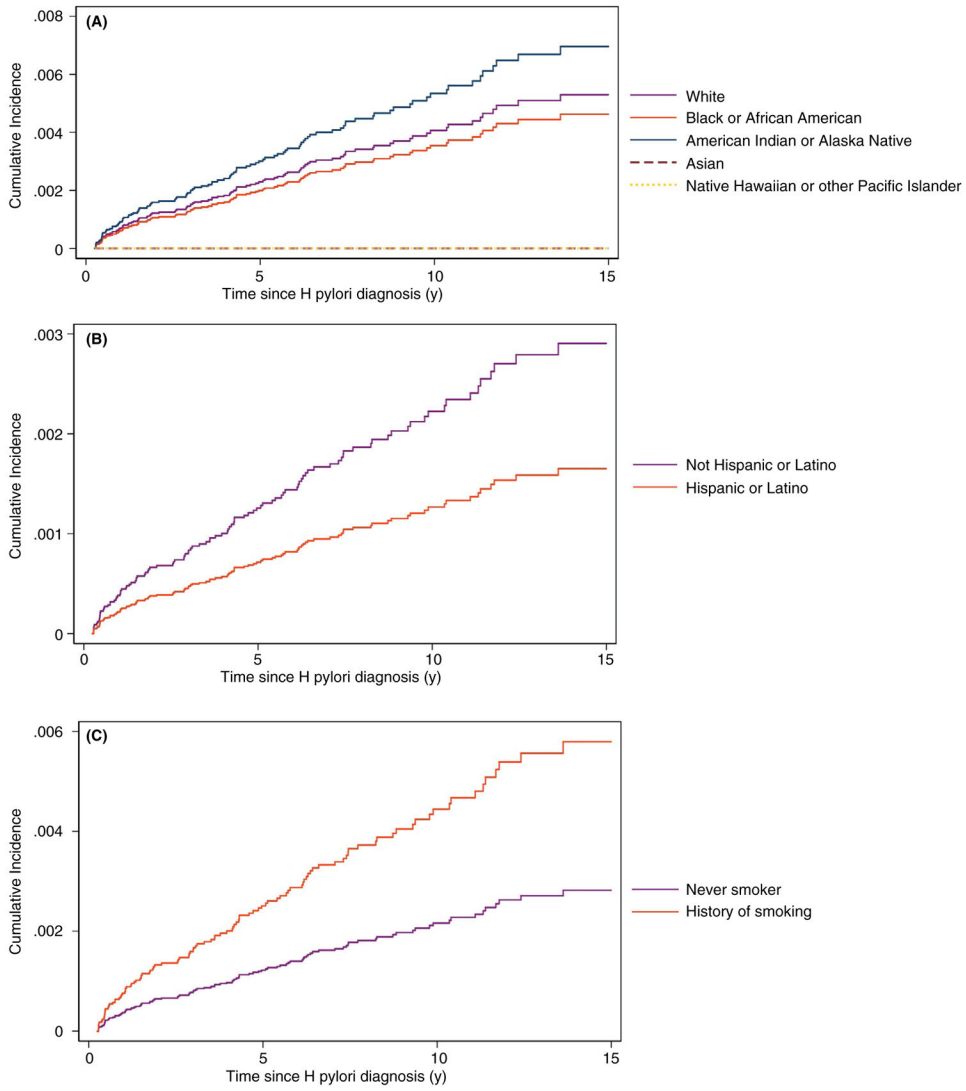

FIGURE 2.

Cumulative incidence curves for oesophageal and proximal gastric cancers by A) race; B) ethnicity; C) smoking, adjusted for other covariates

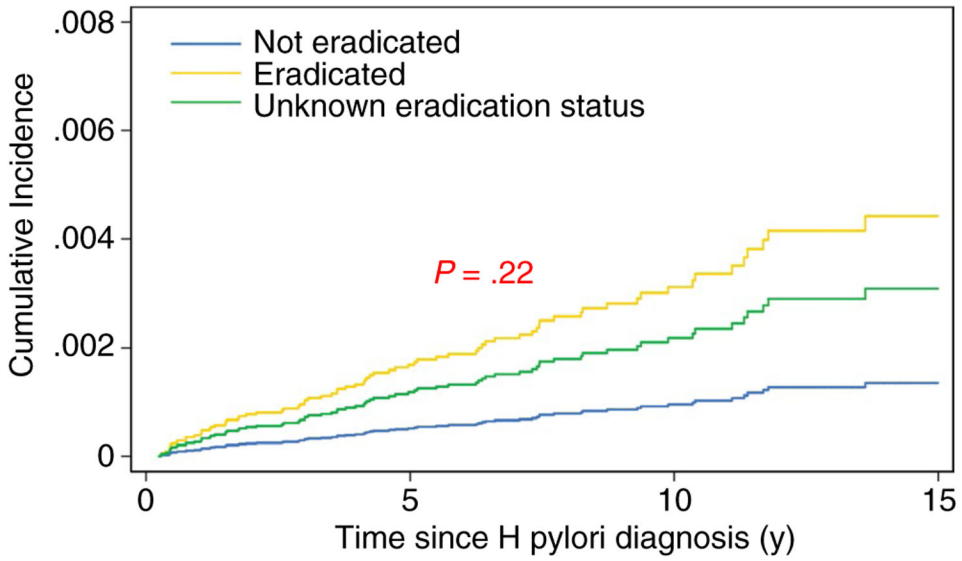

FIGURE 3.

Cumulative incidence curves for the development of future oesophageal and proximal gastric cancers by *Helicobacter pylori* eradication status

TABLE 1

Comparison of patients with *Helicobacter pylori* who did and did not develop oesophageal or proximal gastric cancer

	H pylori **(n = 36 695)**	***H pylori*** **with future oesophageal or proximal gastric cancer (n = 108)**	***P*-value**
Age in years at *H pylori*, median (IQR)	61.6 (52.9, 68.9)	64.5 (58.0, 73.4)	<0.001
Male (%)	33 675 (91.8%)	105 (97.2%)	0.04
Race (%)			0.55
White	15 628 (42.6%)	47 (43.5%)	
Black or African American	11 167 (30.4%)	27 (25.0%)	
American Indian or Alaskan Native	291 (0.8%)	1 (0.9%)	
Asian	213 (0.6%)	0 (0.0%)	
Native Hawaiian/Pacific Islander	295 (0.8%)	0 (0.0%)	
Unknown/declined to answer	9101 (24.8%)	33 (30.6%)	
Ethnicity			0.01
Hispanic/Latino	24 523 (66.8%)	69 (63.9%)	
Not Hispanic or Latino	4140 (11.3%)	5 (4.6%)	
Unknown/declined to answer	8032 (21.9%)	34 (31.5%)	
Ever smoker (%)	9341 (25.5%)	38 (35.2%)	0.02
Method of *H pylori* diagnosis			0.091
Pathology	25 575 (69.7%)	67 (62.0%)	
Stool antigen	10 741 (29.3%)	41 (38.0%)	
Urea breath test	379 (1.0%)	0 (0.0%)	
Received prescription for *H pylori* eradication	27 672 (75.4%)	76 (70.4%)	0.22
Poverty level of zip code where patient resided at *H pylori* diagnosis			0.56
<10% residing below poverty level	7552 (20.6%)	20 (18.5%)	
10%-24.9% residing below poverty level	17 295 (47.1%)	45 (41.7%)	
25%-49.9% residing below poverty level	9177 (25.0%)	34 (31.5%)	
≥50% residing below poverty level	1047 (2.9%)	4 (3.7%)	
Unknown	1624 (4.4%)	5 (4.6%)	
Follow up time in years, median (IQR)	5.1 (2.3, 8.7)	3.4 (1.1, 6.3)	<0.001
Deceased	8331 (22.7%)	16 (84.2%)	<0.001

TABLE 2

Risk factors for the development of oesophageal or gastric cardia cancer using multivariable competing risk time to event model

	SHR (95% CI)	*P*-value
Age at *Helicobacter pylori* diagnosis[a]	1.17 (1.09-1.25)	<0.001
Ethnicity		0.06
Not Hispanic or Latino	Reference	
Hispanic or Latino	0.57 (0.22-1.46)	
Unknown	2.71 (0.93-7.90)	
Race		<0.001
White	Reference	
Black/African American	0.87 (0.53-1.43)	
American Indian/Alaskan Native	1.31 (0.18-9.60)	
Asian	*b*	
Native Hawaiian/Pacific Islander	*b*	
Unknown	0.61 (0.21-1.80)	
History of smoking	2.06 (1.33-3.18)	0.001

Note: Other covariates tested but not included in the final multivariable model as they were not significant ($P \geq .1$) were: gender, whether the patient received prescription for an eradication regimen for *H pylori*, poverty level of patient's zip code of residence at time of *H pylori* diagnosis.

[a] Per 5-year increase of age.

[b] Point estimates and confidence intervals less than 0.000001.