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Association between *Helicobacter pylori* and Barrett's Esophagus: A Case–Control Study

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CONFLICT OF INTEREST

Guarantor of the article: Lori A. Fischbach, MPH, PhD.

Potential competing interest: Lori A. Fischbach received payment by Axcan Pharma (now known as Aptalis Pharma) for speaking at an educational web-seminar. Graham has been a paid consultant by Otshka Pharm Japan and has received royalties related to the urea breath test. Vela has been a board member on an advisory panel sponsored by Given Imaging, has grants pending that have been submitted to the American College of Gastroenterology, and has received payment by Sandhill Scientific and Glaxo Smith Kline for lectures on gastroesophageal reflux disease. Abraham is on the Board of Trustees for the American College of Gastroenterology, has received honoraria from the American College of Gastroenterology and the American Gastroenterological Association for lectures, and has a grant pending that was submitted to Johnson & Johnson. Kramer has grants pending from the VA, NIH, and Baylor.

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Abstract

OBJECTIVES—The estimated association between *Helicobacter pylori* and Barrett's esophagus (BE) has been heterogenous across previous studies. In this study, we aimed to examine the association between *H. pylori* and BE and to identify factors that may explain or modify this association.

METHODS—We conducted a case–control study in which we used screening colonoscopy controls recruited from primary care clinics as our primary control group in order to minimize selection bias. All participants underwent an esophagogastroduodenoscopy with gastric mapping biopsies. We used logistic regression to obtain odds ratios (ORs) and 95 % confidence intervals (CIs) to estimate the association between *H. pylori* and BE while controlling for confounders.

RESULTS—We identified 218 cases and 439 controls. The overall OR for the association between *H. pylori* and BE after controlling for age and white race was 0.55 (95 % CI: 0.35–0.84). We observed an even stronger inverse association (OR: 0.28; 95 % CI: 0.15, 0.50) among participants with corpus atrophy or antisecretory drug use ≥1 time per week (factors thought to lower gastric acidity), and no inverse association in patients without these factors (OR: 1.32; 95 % CI: 0.66, 2.63).

CONCLUSIONS—The association between *H. pylori* and a decreased risk for BE appears to occur in patients with factors that would likely lower gastric acidity (corpus atrophy or taking antisecretory drugs at least once a week).

INTRODUCTION

Esophageal adenocarcinoma is a highly fatal disease (1). In developed countries including the United States, the incidence of esophageal adenocarcinoma has increased in recent years for all races, but especially in non-Hispanic White men (2,3). Barrett's esophagus (BE) is a precancerous lesion for esophageal adenocarcinoma (4,5) but the causal process leading to BE has yet to be elucidated.

Helicobacter pylori, a bacterial infection that colonizes the human gastric mucosa, modulates gastric acid production, which may affect the development of reflux esophagitis, BE, and ultimately esophageal adenocarcinoma (6–10). *H. pylori*, which causes gastric inflammation and atrophy, may in some patients lower acid production in the stomach by damaging the acid-producing parietal cells in the corpus (11). Evidence from meta-analyses and systematic reviews examining the association between *H. pylori* and gastroesophageal reflux disease have tended to show an inverse association, although this association has been shown to be heterogeneous across studies (12–14). Similarly, meta-analyses examining the association between *H. pylori* and BE have shown heterogenous findings across studies (15–17). There is a paucity of evidence evaluating whether histological changes such as corpus gastritis or atrophy and other factors related to gastric acidity could be a source of this heterogeneity.

Therefore, we conducted a case–control study that aimed to examine the association between *H. pylori* and BE using an identifiable base population seeking healthcare within the veterans affiairs (VAs) system in Houston, TX. We also aimed to examine whether factors such as histological changes in the stomach or gastroesophageal reflux disease symptoms could explain this association, and whether corpus gastritis, corpus atrophy, and/or antisecretory medication could modify this association. Cases were those aged 50–80 diagnosed with BE in this VA system, and our primary control group came from individuals from primary care who were eligible (aged 50–80) for a screening colonoscopy in this same VA system. We characterized the extent and severity of gastritis and gastric atrophy by performing systematic gastric mapping biopsies for cases and controls.

METHODS

Study design and study population

To obtain the cases and controls for this study, we first recruited subjects aged 50 years and above seeking healthcare at the Michael E DeBakey Veterans affairs Medical Center (MEDVAMC) in Houston, TX from 1 September 2008 to 31 December 2011. We recruited subjects from consecutive patients identified at primary care facilities in the MEDVAMC system who were eligible for a routine screening colonoscopy and agreed to also undergo an esophagogastroduodenoscopy (EGD) along with their colonoscopy. Our secondary recruitment source was consecutive eligible patients undergoing an elective EGD. We performed gastric mapping by taking seven mucosal biopsy samples from the antrum (from the greater curvature and from the lesser curvature), the corpus (from the distal greater curvature, distal lesser curvature, proximal greater curvature, proximal lesser curvature), and the cardia. Live-case orientation sessions were conducted with the endoscopists to demonstrate landmarks, biopsy sites, and recorded findings regarding suspected BE.

This study was approved by the Institutional Review Boards at both the MEDVAMC and Baylor College of Medicine.

Eligibility criteria for cases and controls

We took at least one biopsy sample from subjects with suspected BE at the site where columnar-appearing mucosa was visually observed between the gastroesophageal junction and the Z-line. We used the Prague CM classification to measure the height of circumferential columnar mucosa in centimeters above the gastroesophageal junction (the *C* value) and the maximum length in centimeters of the columnar mucosa above the gastroesophageal junction (the *M* value) (18). Cases with BE were subjects from the EGD patient group or the screening colonoscopy group who met our eligibility criteria and had intestinal metaplasia confirmed by two pathologists (MR and GV) in their histopathological examination of the biopsy tissue taken at the site where suspected BE was found. These BE assessments were performed blind to the subjects' *H. pylori* status.

We were not able to sample from all primary care patients because of the large number of patients seen at the MEDVAMC. Therefore, we recruited subjects from seven participating primary care clinics who were eligible for a screening colonoscopy for our "screening

colonoscopy" control group. We screened electronic medical records for all patients scheduled for an appointment with their primary care provider to determine eligibility for screening colonoscopy (aged 50–80 and no colonoscopy in the previous 3 years) and invited them to undergo an EGD along with their colonoscopy. Endoscopy controls included all consecutive endos-copy controls scheduled for elective upper endoscopy who met our inclusion criteria, and agreed to participate in the study but were not diagnosed with BE.

Between 1 September 2008 and 31 December 2011, all cases and controls met the inclusion criteria of (1) being 50–80 years of age; (2) completing an EGD examination with gastric mapping biopsies; and (3) provided informed consent. In addition, none of the eligible subjects had any of the following exclusion criteria: (1) previous gastroesophageal surgery; (2) previous esophageal, lung, liver, colon, breast, or stomach cancer; (3) current use of anticoagulants; (4) platelet counts <70,000, ascites, or known gastroesophageal varices; or (5) history of major stroke or a mental condition that could inhibit our ability to obtain valid information from the interview. Subjects in the controls groups were also excluded if they were diagnosed with definitive or suspected BE during the study EGD examination.

Measurement of *H. pylori* gastritis, and atrophy

Biopsy specimens were stained with: (1) hematoxylin and eosin; (2) a modified silver stain; and (3) an alcian blue-Periodic acid Schiff stain to detect prevalent *H. pylori* infection. In all cases where there was a low density of silver-stained organisms, their identity was confirmed by immunohistochemical staining. Biopsies were examined and graded by two gastrointestinal pathologists (MR and GV). Features of gastritis and gastric atrophy were identified and graded according to the standardized operative link for gastritis assessment system (19), which uses the updated Sydney System (20). Prevalent *H. pylori* status was determined blind to the subjects' BE diagnosis and was classified as positive if the organism was histologically observed in any of the gastric biopsies.

As part of our sensitivity analyses, we randomly selected 285 (60%) subjects classified as *H. pylori* negative by histology in the primary analysis for further culture of their gastric samples. Frozen specimens were thawed and the tissue was homogenized and inoculated onto two types of selective media, Brain Heart Infusion and *H. pylori* Special Peptone Agar plates with 7% horse blood. The plates were incubated at 37°C under microaerophilic conditions. The negative plates were reincubated and then read every 24 h for up to 14 days. Positive growth was transferred to a fresh, nonselective Brain Heart Infusion blood agar plate, and then incubated for 48–72 h. *H. pylori* was identified by culture when the oxidase, catalase, and urease reactions were positive with a compatible Gram-negative stain. A subject was considered definitively positive for *H. pylori* if *H. pylori* was identified as positive either by histology or culture.

Measurement of other covariates

We interviewed all study participants before the EGD to collect data on relevant covariates such as age, gender, race, the onset, frequency, and severity of symptoms of gastroesophageal reflux disease using the Gastroesophageal Reflux Questionnaire (21), current and previous smoking status, dietary intake, and frequency of medication use such as

proton pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs). The frequency of dietary intake of fruits and vegetables was obtained using the Block Food Frequency Questionnaire (22). Height and weight was also measured before endoscopy to determine the body mass index.

Analysis

We first performed descriptive analyses for the study population using χ^2-tests to compare the cases and screening colonos-copy controls with regard to demographic variables, smoking, obesity, symptoms, medication use, and histological factors. For the primary analysis, we compared cases and screening colon-oscopy controls using logistic regression to obtain odds ratios (ORs) and 95% confidence intervals (CIs) to estimate the association between *H. pylori* and BE while controlling for age and non-Hispanic white race as potential confounders. Further adjustment for black race, gender, obesity, smoking, nonsteroidal anti-inflammatory medications, and dietary factors were controlled for if they changed the estimates by > 10% (23). In addition, we used logistic regression models to estimate the association between histological changes in the stomach and BE. We then examined whether histological changes in the stomach and/or gastroesophageal reflux disease symptoms could explain the association between *H. pylori* and BE by adding these variables to the model containing *H. pylori*. We also examined whether factors that affect gastric-acid secretion such as corpus gastritis, corpus atrophy, and/or antisecretory medication could modify the association between *H. pylori* and BE by using stratified logistic regression models, likelihood ratio tests in nested models, and linear binomial regression to assess additive interaction while adjusting for confounders. As our analyses focused on achieving our study aims, no multiple comparison adjustments were made, as others have discussed in detail elsewhere that such adjustment is not relevant and would produce inappropriately imprecise estimates (24,25). The analyses were also conducted for short-segment and long-segment BE separately. Cases with BE whose *C* value or *M* value was ≥3 were classified as long-segment BE, whereas those whose C-value and M-value was <3 were classified as short-segment BE (26).

We conducted sensitivity analyses to evaluate the robustness of our estimates. As mentioned previously, bacterial culture of gastric samples was performed in randomly selected subjects classified as *H. pylori* negative based on histology. Additional sensitivity analyses were performed using a control group from the cross-sectional study of endoscopy patients without BE (‘upper endoscopy control group’) who met the eligibility criteria. As patients referred for an upper endoscopy may recall information (for example, medication use, dietary information, and symptoms) differently than participants from the screening colonos-copy group, we compared the estimated association using the screening colonoscopy controls with the estimated association using the upper endoscopy controls.

RESULTS

We identified 218 eligible cases with BE; 133 (61.0%) were classified as short-segment BE and 85 (39.0%) were classified as long-segment BE. Out of 1,424 patients who were invited to also undergo an EGD along with their screening colonos-copy, 380 did not fulfill our

eligibility criteria, 287 refused to participate, and 318 did not show up for their EGD appointment. Therefore, 42% (439 participants) of the 1,044 eligible screening colonoscopy controls whom we invited to participate were enrolled in our study. The cases and controls are descriptively compared in **Tables 1A** and **B**. The vast majority of participants were men for both cases and controls, which was expected in this VA population (97.3% for cases and 96.6% for controls). Overall, the study population consisted of 66.4% non-Hispanic white participants; there were more non-Hispanic white participants in the case group (87.2%) compared with the controls (56.0%), and thus more African Americans among the controls (41.7%) compared with cases (11.9%). Approximately half of all cases (51.4%) and controls (47.8%) were obese. Most cases and controls were either current smokers (23% and 25%, respectively) or former smokers (46.5 and 48.3%, respectively). Cases were more likely to report frequent symptoms (> 1 times per week) of heartburn and acid regurgitation compared with controls (35.8 vs. 20.1%). Similarly, cases were more likely to report frequently taking (> 1 times per week) PPIs (71.3 vs. 22.8%) and H2RAs (10.5 vs. 5.5%) compared with controls.

H. pylori infection was identified in 16.1% of cases and 33.3% of controls ($P<0.0001$). Only 2 of 181 (1.1%) *H. pylori* -positive subjects whose biopsies were cultured were positive using culture alone. We compared the gastric histological features of cases and controls (**Table 1B**). The proportions of subjects with gastritis are those of the total population and not of the *H. pylori*-positive subjects. Corpus gastritis was consistently present less frequently among cases compared with controls (17.9 vs. 32.4%); this difference was mostly explained by difference in severe corpus gastritis (14.7 vs. 27.1%). Gastritis was only observed more frequently (although not significantly more) among cases vs. controls for grade 1 antral gastritis and gastritis, which was exclusively found in the antrum. Atrophy was observed less frequently among the cases with BE compared with the controls (18.4 vs. 28.7%). Similarly, corpus atrophy was less frequently observed in cases vs. controls (11.5 vs. 18.7%).

Results of our overall logistic regression analyses yielded an OR showing *H. pylori* to be inversely associated with BE after controlling for age and non-Hispanic white race (OR: 0.55; 95% CI: 0.35–0.84) (**Table 2**). The addition of black race to the model did not alter the OR estimate (OR: 0.55; 95% CI: 0.35–0.85). Other variables also did not substantially change the OR estimate (**Table 2**). Therefore, all subsequent models contained age and non-Hispanic white race. In sensitivity analyses, similar results were obtained using endoscopy controls (**Table 2**). Only two (<1%) subjects who were classified as *H. pylori* negative based on histology and who had further bacterial culture results were identified as positive for *H. pylori* using culture. Our results were similar for analyses that included histology alone vs. histology and available culture results. Therefore, unless specified otherwise, we report results using colonoscopy controls and all available data on *H. pylori* status.

The overall estimates fairly consistently showed an inverse association between *H. pylori* and different lengths of BE, although a slightly stronger inverse association was observed for long-segment BE (**Table 3**). The OR was 0.61 (95% CI: 0.37–1.01) for short-segment BE and 0.40 (95% CI: 0.19, 0.81) for long-segment BE. When we estimated the association between histological changes in the stomach and BE, we observed that these tended to show

stronger inverse associations between the histological change and long-segment BE compared with short-segment BE (**Table 3**). The OR for the estimated association between corpus gastritis and BE was 0.42 (95% CI: 0.21–0.86) and 0.82 (95% CI: 0.50–1.32) for long-segment and short-segment BE, respectively. Similar associations were observed for antral active and chronic gastritis. Similarly, the OR for the estimated association between any atrophy and BE was 0.65 (95% CI: 0.34–1.26) and 0.86 (95% CI: 0.52–1.26) for long- and short-segment BE, respectively.

We added to the model putative intermediates in the causal pathway whereby *H. pylori* may affect BE to evaluate whether they could attenuate and hence explain the inverse association between *H. pylori* and BE (**Table 4**). When gastritis, especially corpus gastritis, was added to the model, the OR for the association between *H. pylori* and BE was attenuated to 0.79 (95% CI: 0.47–1.31).

Table 5, **Appendices Tables A1–G1** and **A2–G2** present the results of our analyses of effect modification. When we estimated the adjusted ORs by PPI or H2RA use, we observed an inverse but nonsignificant association between *H. pylori* and BE among those using a PPI or H2RA≥1 times per week (OR: 0.56; 95% CI: 0.27, 1.14), and did not observe a strong inverse association among those who were not taking these medication or taking them less than weekly (OR: 0.90; 95% CI: 0.49, 1.66). When we stratified the adjusted OR separately by corpus atrophy or corpus gastritis, we did not observe obvious effect modification using a multiplicative model. However, when we stratified the OR by corpus atrophy or antisecretory drug use (≥1 time per week), we observed a strong inverse association between *H. pylori* and BE among those with corpus atrophy or antisecretory use (OR: 0.28; 95% CI: 0.15, 0.50) and did not observe an inverse association between *H. pylori* and BE in the strata without these factors (OR: 1.32; 95% CI: 0.66, 2.63); likelihood ratio tests suggested multiplicative interaction (P=0.0006) in nested models. We did not observe additive interaction between *H. pylori* and either corpus gastritis or corpus atrophy separately or in combination (**Appendices Tables B2,C2** and **F2**). However, we did observe additive interaction between *H. pylori* and the use of antisecretory medication in unadjusted models, and between *H. pylori* and corpus, atrophy or antisecretory drugs in unadjusted and adjusted models (**Appendices Tables A2** and **D2**).

DISCUSSION

Overall, our results are consistent with the hypothesis that being infected with *H. pylori* is inversely associated with BE. Even after controlling for potential confounding by age and non-Hispanic White race, we estimated that the odds of observing prevalent *H. pylori* was approximately half among cases with BE compared with controls without BE. The overall inverse association between *H. pylori* and BE was observed in both control groups (screening colonoscopy or upper endoscopy controls) and wi Theither long-segment or short-segment BE as the outcome. However, the strong inverse association between *H. pylori* and BE was restricted to patients with corpus atrophy or to those who had regularly taken antisecretory medications, which would likely suppress gastric acid secretion.

We also observed that the presence of corpus gastritis was inversely associated with the presence of BE. Corpus gastritis also partially explained the association between *H. pylori* and BE. These findings are consistent with other evidence showing *H. pylori* infection causes inflammation in the stomach, which could inhibit acid production in the corpus of the stomach (11,27). Lower acid production in the stomach would decrease the likelihood of damaging acid reflux into the esophagus, thus leading to protective effects on disease outcomes in the esophagus. There was a strong association between the presence of corpus gastritis and that of antral gastritis, and therefore we observed similar associations between antral gastritis and BE, and gastritis overall and BE. We also observed a strong association between *H. pylori* infection and corpus gastritis, which resulted in small cell sizes in stratified analyses involving these variables. For example, only 11 subjects (2 cases and 9 controls) without corpus gastritis were infected with *H. pylori*, which resulted in unstable estimates in the assessment of effect modification involving corpus gastritis (**Appendices Tables C1, E1–G1**).

Corpus atrophy may also damage the acid-producing parietal cells that could reduce acid exposure to the esophagus, and therefore this variable would also be expected to attenuate the association between *H. pylori* and BE (28). However, we did not observe attenuation of the association between *H. pylori* and BE by corpus atrophy. One reason we may not have been able to observe attenuation of *H. pylori* on BE by corpus atrophy may be owing to misclassification of atrophic gastritis because of its patchy distribution (29). Although intestinal metaplasia may provide a better measure of glandular loss, we also did not observe attenuation of the *H. pylori*– BE association by intestinal metaplasia. Both advancing atrophic gastritis and intestinal metaplasia may lead to the disappearance of *H. pylori* (30), which may have compromised our ability to observe these lesions as intermediate factors influencing the association between *H. pylori* and BE. Furthermore, the cross-sectional nature of the current study with prevalent *H. pylori* and prevalent histological variables prevented an examination of the temporal relation between *H. pylori* infection, possible intermediate or modifying factors and BE.

Corpus atrophy or frequent use of a PPI or an H2RA modified the association between *H. pylori* and BE. These findings could suggest that the existence of corpus atrophy or use of acid-suppressive medication potentiates the protective effect of *H. pylori* on BE. However, we also observed that *H. pylori* infection was more likely to be detected among participants who were not taking a PPI compared with those who were (34.1% vs. 15.3%). Previous studies have observed that PPIs can suppress *H. pylori* infection, leading to misclassifying *H. pylori* as absent when it is present (31). However, we used multiple samples from both the antrum and the corpus to detect *H. pylori*, which would have minimized such misclassification (32). We also used gastric tissue culture to test for *H. pylori* in randomly selected subjects classified as *H. pylori* negative by histology, which identified only two (<1%) additional subjects with *H. pylori*. Furthermore, misclassification of *H. pylori* due to PPI use biasing the association of *H. pylori* and BE would have likely occurred for both cases and controls taking a PPI, which would have resulted in a biased null association, and therefore would not explain the strong inverse association between *H. pylori* and BE among those with corpus atrophy or taking acid suppression medication.

Our current findings add to the existing examination of the association between *H. pylori* and BE, and the evaluation of whether histological and other factors related to gastric acidity could explain or modify the association between *H. pylori* and BE. As described in previous meta-analyses, previous studies have reported heterogenous findings (15–17). In the meta-analysis by Wang *et al.* (16), significant heterogeneity in the association of *H. pylori* and BE was also observed across studies, and this heterogeneity was explained by the type of controls selected and the location of the study being conducted in Asia. We also observed in our recent meta-analysis that, because of the manner in which the non-BE controls were selected, most existing studies examining the association between *H. pylori* and BE had potential sources of selection bias (15). Therefore, we selected controls from subjects who were eligible for a screening colonoscopy to estimate subjects who if they were to have BE would be diagnosed with BE in this same VA base population. However, in the current investigation, no obvious selection bias was observed for the endoscopy controls, as the results for both types of control groups were similar. Nevertheless, our results are similar to results from four studies identified in our meta-analysis with identifiable base populations that also used gastric tissue to diagnose *H. pylori* (15), and with recent findings from a case–control study by Rubenstein *et al.* (33) using colorectal cancer screening controls in Michigan. The OR estimate overall from the Michigan study was 0.53 (95% CI: 0.29–0.97) compared with 0.55 (95% CI: 0.35–0.84) in our study. The study by Rubenstein *et al.* (33) also reported an even stronger inverse association between CagA-positive strains of *H. pylori* and BE (0.36; 95% CI: 0.14–0.90).

Although the current study was designed to minimize potential biases such as selection bias and confounding, selection bias in the form of self-selection bias could have occurred as only 42% of the eligible screening colonoscopy controls whom we invited to participate actually enrolled in our study. If correlates of *H. pylori* infection, such as socioeconomic status, influenced participation in the study differently for cases and controls, then this could have led to selection bias.

As we have already discussed, our study limitations also include potential misclassification of *H. pylori* in the presence of PPI use and advancing atrophic gastritis. Even after controlling for age and non-Hispanic white race, residual confounding may have occurred for potential confounding factors such as fruit and vegetable intake. Data regarding the intake of fruits and vegetables were missing for 42% of the subjects, and therefore this variable was not controlled for in our primary analyses. However, the estimated association between *H. pylori* and BE was similar with or without the inclusion of fruit and vegetable intake in the model (OR: 0.55 without fruit and vegetable intake, and OR: 0.52 with fruit and vegetable intake), and therefore it is unlikely fruit and vegetable intake confounded the estimates in our study.

Our study is also limited by the measurement of prevalent *H. pylori*. Therefore, we do not know whether *H. pylori* affects the occurrence of BE or *vice versa*. However, as *H. pylori* infection is primarily initially acquired during childhood (34), it is more likely that *H. pylori* infection preceded BE.

Finally, our study was conducted in a study population aged 50–80 years from the MEDVAMC in Houston TX, which consisted primarily of males, and therefore our results are not generalizable to females, or patients under age 50. In addition, our study population was more likely to smoke, be obese, and was slightly more likely to be white non-Hispanic (66.4%) as compared with the general population of the United States (35), which further limits the generalizability of our findings.

Conclusion

Overall, we observed that the presence of *H. pylori* was inversely associated with BE in a primarily male population, and this inverse association was observed to be restricted to subjects who have characteristics that lower gastric-acid production such as corpus atrophy or use of antisecretory medication on a weekly basis. The odds of BE was estimated to be approximately half as much among *H. pylori* -infected individuals compared with those without *H. pylori* infection.

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Appendix

Table A1

Numbers of subjects with and without *Helicobacter pylori* infection, and weekly use of H2RAs or PPI for BE cases and controls

Weekly use (or more) of H2RAs or PPI	*H. pylori* infection	Number of patients with BE	Number of patients without BE
Yes	Yes	17	29
	No	135	83
No	Yes	18	117
	No	48	210

BE, Barrett's esophagus; H2RA, H2 receptor antagonist; PPI, proton pump inhibitor.

Table A2

Assessment of additive interaction between *Helicobacter pylori* and weekly use (or more) of H2RA or PPI on BE

Variable	Estimate (s.e.)	Wald χ^2 (*P* value)[a]
Unadjusted		
H. pylori	–0.05 (0.04)	1.93 (0.17)
Use of H2RA or PPI	0.43 (0.04)	112.5 (<0.0001)
Interaction between *H. pylori* and H2RA/PPI use	–0.20 (0.09)	5.11 (0.02)
Adjusted[a]		
H. pylori	–0.03 (0.04)	0.58 (0.44)
Use of H2RA or PPI	0.39 (0.04)	84.3 (<0.0001)

Variable	Estimate (s.e.)	Wald χ^2 (*P* value)[a]
Interaction between *H. pylori* and H2RA/PPI use	–0.15 (0.09)	3.19 (0.07)

BE, Barrett's esophagus; H2RA, H2 receptor antagonist; PPI, proton pump inhibitor.

[a]Controlling for age and non-Hispanic white race.

Table B1

Numbers of subjects with or without *Helicobacter pylori* infection and corpus atrophy for cases with BE and controls

Corpus atrophy	*H. pylori* infection	Number of patients with BE	Number of patients without BE
Yes	Yes	12	56
	No	13	26
No	Yes	23	90
	No	170	267

BE, Barrett's esophagus.

Table B2

Assessment of additive interaction between *Helicobacter pylori* and corpus atrophy on BE

Variable	Estimate (s.e.)	Wald χ^2 (*P* value)[a]
Unadjusted		
H. pylori	–0.19 (0.04)	17.4 (<0.0001)
Corpus atrophy	–0.06 (0.08)	0.50 (0.48)
Interaction between *H. pylori* and corpus atrophy	0.03 (0.10)	0.08 (0.77)
Adjusted[a]		
H. pylori	–0.11 (0.05)	5.54 (0.02)
Corpus atrophy	0.0074 (0.07)	0.01 (0.92)
Interaction between *H. pylori* and corpus atrophy	0.03 (0.09)	0.15 (0.70)

BE, Barrett's esophagus.

[a]Controlling for age and non-Hispanic white race.

Table C1

Numbers of subjects with or without *Helicobacter pylori* infection and corpus gastritis for cases with BE and controls

Corpus gastritis	*H. pylori* infection	Number of patients with BE	Number of patients without BE
Yes	Yes	33	137
	No	39	116
No	Yes	2	9
	No	144	177

BE, Barrett's esophagus.

Table C2

Assessment of additive interaction between *Helicobacter pylori* and corpus gastritis on BE

Variable	Estimate (s.e.)	Wald χ^2 (*P* value)[a]
Unadjusted		
H. pylori	–0.27 (0.12)	4.78 (0.03)
Corpus gastritis	–0.20 (0.05)	19.54 (<0.0001)
Interaction between *H. pylori* and corpus gastritis	0.21 (0.13)	2.67 (0.10)
Adjusted[a]		
H. pylori	–0.23 (0.15)	2.31 (0.13)
Corpus gastritis	–0.13 (0.05)	7.95 (0.005)
Interaction between *H. pylori* and corpus gastritis	0.22 (0.16)	1.89 (0.17)

BE, Barrett's esophagus.

[a]Controlling for age and non-Hispanic white race.

Table D1

Numbers of subjects with or without *Helicobacter pylori* infection and corpus atrophy, H2RAs, or PPIs

Corpus atrophy or weekly acid reduction medication (H2RA or PPI)	*H. pylori* infection	Number of patients with BE	Number of patients without BE
Yes	Yes	20	76
	No	139	103
No	Yes	15	70
	No	44	190

BE, Barrett's esophagus; H2RA, H2 receptor antagonist; PPI, proton pump inhibitor.

Table D2

Assessment of additive interaction between *Helicobacter pylori* and corpus atrophy or acid reduction medication (weekly H2RA or PPI use) on BE

Variable	Estimate (s.e.)	Wald χ^2 (*P* value)[a]
Unadjusted		
H. pylori	–0.01 (0.05)	0.06 (0.81)
Corpus atrophy or weekly acid reduction medication (H2RA or PPI)	0.39 (0.05)	89.8 (<0.0001)
Interaction between *H. pylori* and corpus atrophy or weekly acid reduction medication	–0.29 (0.07)	18.2 (<0.0001)
Adjusted[a]		
H. pylori	0.01 (0.05)	0.05 (0.83)
Corpus atrophy or weekly acid reduction medication (H2RA or PPI)	0.34 (0.04)	68.9 (<0.0001)
Interaction between *H. pylori* and corpus atrophy or weekly acid reduction medication	–0.35 (0.07)	24.7 (<0.0001)

BE, Barrett's esophagus; H2RA, H2 receptor antagonist; PPI, proton pump inhibitor.

[a]Controlling for age and non-Hispanic white race.

Table E1

Numbers of subjects with or without *Helicobacter pylori* infection and corpus gastritis, H2RAs, or PPIs

Corpus gastritis or weekly acid reduction medication (H2RA or PPI)	*H. pylori* infection	Number of patients with BE	Number of patients without BE
Yes	Yes	34	141
	No	154	167
No	Yes	1	5
	No	29	129

BE, Barrett's esophagus; H2 receptor antagonist; PPI, proton pump inhibitor.

Table E2

Assessment of additive interaction between *Helicobacter pylori* and corpus gastritis or acid reduction medication (weekly H2RA or PPI use) on BE

Variable	Estimate (s.e.)	Wald χ^2 (*P* value)[a]
Unadjusted		
H. pylori	–0.02 (0.16)	0.02 (0.90)
Corpus gastritis or weekly acid reduction medication (H2RA or PPI)	0.29 (0.04)	48.7 (<0.0001)
Interaction between *H. pylori* and corpus gastritis or weekly acid reduction medication	–0.27 (0.16)	2.72 (0.10)
Adjusted[a]		
H. pylori	–0.03 (0.02)	0.02 (0.88)
Corpus gastritis or weekly acid reduction medication (H2RA or PPI)	0.25 (0.04)	39.8 (<0.0001)
Interaction between *H. pylori* and corpus gastritis or weekly acid reduction medication	–0.16 (0.21)	0.52 (0.47)

BE, Barrett's esophagus; H2RA, H2 receptor antagonist; PPI, proton pump inhibitor.

[a]Controlling for age and non-Hispanic white race.

Table F1

Numbers of subjects with or without *Helicobacter pylori* infection and corpus gastritis or corpus atrophy

Corpus atrophy or corpus gastritis	*H. pylori* infection	Number of patients with BE	Number of patients without BE
Yes	Yes	33	137
	No	44	121
No	Yes	2	9
	No	139	172

BE, Barrett's esophagus.

Table F2

Assessment of additive interaction between *Helicobacter pylori* and corpus gastritis or corpus atrophy on BE

Variable	Estimate (s.e.)	Wald χ^2 (*P* value)[a]
Unadjusted		
H. pylori	–0.27 (0.12)	4.91 (0.03)
Corpus gastritis or corpus atrophy	–0.18 (0.05)	16.4 (<0.0001)
Interaction between *H. pylori* and corpus gastritis or corpus atrophy	0.19 (0.13)	2.26 (0.13)
Adjusted[a]		
H. pylori	–0.23 (0.16)	2.2 (0.14)
Corpus gastritis or corpus atrophy	–0.12 (0.05)	6.98 (0.0083)
Interaction between *H. pylori* and corpus gastritis or corpus atrophy	0.21 (0.16)	1.70 (0.19)

BE, Barrett's esophagus.

[a]Controlling for age and non-Hispanic white race.

Table G1

Numbers of subjects with or without *Helicobacter pylori* infection and corpus gastritis, corpus atrophy or H2RAs, or PPIs

Corpus gastritis, corpus atrophy, H2RA or PPI use	*H. pylori* infection	Number of patients with BE	Number of patients without BE
Yes	Yes	34	141
	No	155	169
No	Yes	1	5
	No	28	124

BE, Barrett's esophagus; H2 receptor antagonist; PPI, proton pump inhibitor.

Table G2

Assessment of additive interaction between *Helicobacter pylori* and corpus gastritis, corpus atrophy, or acid reduction medication (weekly H2RA or PPI use) on BE

Variable	Estimate (s.e.)	Wald χ^2 (*P* value)[a]
Unadjusted		
H. pylori	–0.02 (0.16)	0.01 (0.09)
Corpus gastritis, corpus atrophy or weekly acid reduction medication (H2RA or PPI)	0.29 (0.04)	49.2 (<0.0001)
Interaction between *H. pylori* and corpus gastritis, corpus atrophy or weekly acid reduction medication	–0.27 (0.16)	2.75 (0.10)
Adjusted[a]		
H. pylori	–0.03 (0.21)	0.02 (0.88)
Corpus gastritis, corpus atrophy or weekly acid reduction medication (H2RA or PPI)	0.25 (0.04)	39.8 (<0.0001)
Interaction between *H. pylori* and corpus gastritis, corpus atrophy or weekly acid reduction medication	–0.16 (0.21)	0.52 (0.47)

BE, Barrett's esophagus; H2RA, H2 receptor antagonist; PPI, proton pump inhibitor.

[a]Controlling for age and non-Hispanic white race.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ *Helicobacter pylori* infection may reduce the risk of Barrett's esophagus (BE).
- ✓ Studies examining the association between *H. pylori* infection and BE have reported heterogenous findings.
- ✓ There is a paucity of evidence evaluating whether histological and other factors related to gastric acidity could explain or modify the association between *H. pylori* and BE.

WHAT IS NEW HERE

- ✓ The odds of having *H. pylori* among cases of BE was approximately one half the odds of having *H. pylori* among the controls without BE.
- ✓ Among subjects with corpus atrophy or frequent use of antisecretory medication, the odds of having *H. pylori* among cases of BE was approximately one quarter the odds of having *H. pylori* among the controls without BE.
- ✓ The absence of *H. pylori* infection is associated with BE, especially among patients with corpus atrophy or using antisecretory medications.

Table 1

(A) Description of BE cases and screening colonoscopy controls without BE[a]; (B) histological characteristics of BE cases and screening colonoscopy controls without BE[b]

Characteristics[a]	Cases	Controls	*P* value[c]
(A)			
Total sample size	218	439	
Age mean (s.d.)	63.2 (5.7)	62.4 (6.6)	0.12
% Males	97.3	96.6	0.65
% Black/African-American	11.9	41.7	<0.0001
% Non-Hispanic White	87.2	56.0	<0.0001
% Hispanic	8.3	9.6	0.58
% H. pylori	16.1	33.3	<0.0001
% Obese	51.4	47.8	0.39
Mean total cigarette pack years	29.2	22.4	0.0047
GERD symptoms ≥1 per week	35.8	20.1	<0.0001
% PPI use > 1 per week	71.3	22.8	<0.0001
% H2-receptor antagonist > 1 per week	10.5	5.5	0.03
% PPI or H2-receptor antagonist > 1 per week	75.7	27.8	<0.0001
Mean duration of weekly GERD symptoms (years)	19.6	7.2	<0.0001
% At least weekly GERD symptoms or acid suppression therapy	73.4	32.6	<0.0001
Mean NSAID intake per week in the past 1 year	3.0 (1.9)	3.2 (1.9)	0.18
(B)			
H. pylori (%)	16.1	33.3	<0.0001
Corpus atrophy (%)	11.5	18.7	0.02
Antral atrophy (%)	10.6	18.2	0.02
Overall gastric atrophy (%)	18.4	28.7	0.0004
Active corpus gastritis			
Grade 1 (%)	6.9	12.1	0.04
Grade 2 (%)	10.1	19.1	0.003
Any active corpus gastritis (%)	17.0	31.2	<0.0001
Active antral gastritis			
Grade 1 (%)	8.7	13.2	0.09
Grade 2 (%)	7.3	16.9	0.0008
Any active antral gastritis (%)	16.1	30.1	0.0001
Chronic corpus gastritis			
Grade 1 (%)	20.6	34.6	0.0002
Grade 2 (%)	12.4	23.0	0.001
Any chronic corpus gastritis (%)	33.0	57.6	<0.0001
Chronic antral gastritis			
Grade 1 (%)	20.6	28.0	0.04
Grade 2 (%)	6.4	20.3	<0.0001

Characteristics[a]	Cases	Controls	*P* value[c]
Any chronic antral gastritis (%)	27.1	48.3	<0.0001
Any corpus gastritis			
Grade 1 (%)	3.2	5.2	0.24
Grade 2 (%)	14.7	27.1	0.0004
Any grade (%)	17.9	32.4	<0.0001
Any antral gastritis			
Grade 1 (%)	6.4	5.9	0.80
Grade 2 (%)	10.1	24.6	<0.0001
Any grade (%)	16.5	30.5	0.0001
Exclusive antral gastritis (%)	6.4	5.5	0.62
Any active gastritis (%)	19.7	33.7	0.0002
Any chronic gastritis (%)	39.5	62.9	<0.0001

BE, Barrett's esophagus; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

[a] Most exposure information came from questions regarding exposures 1+ year before endoscopy.

[b] IM, intestinal metaplasia.

[c] *P* value derived from χ^2-tests.

Table 2

Estimates for the effect of *Helicobacter pylori* on Barrett's esophagus[a]

	Screening colonoscopy controls *N*=439		Endoscopy controls *N*=822	
Model adjusted for	**OR**	**95% CI**	**OR**	**95% CI**
Age and White race[b]	0.55	0.35–0.84	0.55	0.33–0.91
Age, White, and Black race	0.55	0.35–0.85	0.56	0.34–0.92
Age, White race, and gender	0.55	0.35–0.84	0.55	0.33–0.91
Age, White race, and smoking (pack years)	0.55	0.34–0.88	0.56	0.33–0.96
Age, White race, and obesity	0.55	0.35–0.85	0.56	0.34–0.94
Age, White race, and NSAID intake	0.53	0.33–0.84	0.57	0.34–0.96

CI, confidence interval; *N*, number of subjects; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

[a] The estimates were generated from logistic regression models comparing BE cases (*N*=218) to either screening colonoscopy controls or endoscopy controls. All cases and controls underwent study esophagogastroduodenoscopy.

[b] Non-Hispanic white race.

Table 3

Estimates for the effect of histological end points related to *Helicobacter pylori* on BE overall, short-segment BE and long-segment BE

	BE overall cases (*N*=218)		BE short-segment cases (*N*=133)		BE long-segment cases (*N*=85)	
Exposure	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
H. pylori	0.55	0.35–0.84	0.61	0.37–1.01	0.40	0.19–0.81
Atrophy						
Corpus	0.78	0.45–1.34	0.79	0.44–1.42	0.59	0.27–1.31
Antrum	0.79	0.46–1.34	1.00	0.56–1.80	0.42	0.16–1.12
Atrophy overall	0.79	0.52–1.22	0.86	0.52–1.41	0.65	0.34–1.26
Active gastritis						
Corpus grade 1	0.76	0.40–1.43	0.82	0.39–1.71	0.74	0.27–2.02
Corpus grade 2	0.66	0.39–1.12	0.82	0.45–1.46	0.39	0.18–0.84
Any in the corpus	0.66	0.43–1.02	0.79	0.48–1.29	0.44	0.22–0.90
Antral grade 1	1.00	0.55–1.81	1.08	0.55–2.11	0.84	0.33–2.11
Antral grade 2	0.52	0.28–0.93	0.64	0.32–1.21	0.33	0.11–0.94
Any in the antrum	0.67	0.43–1.04	0.77	0.47–1.29	0.48	0.24–0.99
Exclusively in the antrum	1.25	0.43–3.67	1.04	0.27–4.00	1.92	0.47–7.90
Chronic gastritis						
Corpus grade 1	0.57	0.38–0.85	0.64	0.40–1.01	0.43	0.23–0.80
Corpus grade 2	0.66	0.40–1.07	0.74	0.43–1.29	0.50	0.23–1.11
Any in the corpus	0.49	0.34–0.71	0.58	0.38–0.87	0.36	0.21–0.62
Antral grade 1	0.74	0.49–1.12	0.72	0.44–1.17	0.76	0.42–1.36
Antral grade 2	0.42	0.23–0.79	0.58	0.30–1.12	0.16	0.04–0.67
Any in the antrum	0.55	0.38–0.80	0.59	0.38–0.91	0.47	0.27–0.82
Exclusively in the antrum	1.14	0.56–2.34	1.09	0.46–2.55	1.25	0.47–3.29
Any gastritis						
Corpus grade 1	0.91	0.36–2.29	1.04	0.37–2.93	0.86	0.18–4.07
Corpus grade 2	0.64	0.41–1.02	0.79	0.47–1.32	0.39	0.18–0.84
Any in the corpus	0.66	0.43–1.02	0.82	0.50–1.32	0.42	0.21–0.86
Antral grade 1	1.40	0.68–2.90	1.42	0.62–3.22	1.23	0.43–3.50
Antral grade 2	0.51	0.31–0.86	0.64	0.36–1.14	0.30	0.12–0.78
Exclusively in the antrum	1.12	0.55–2.29	1.07	0.46–2.49	1.24	0.47–3.26
Any in the antrum	0.67	0.43–1.05	0.79	0.48–1.31	0.47	0.23–0.97
Any gastritis	0.53	0.37–0.75	0.59	0.39–0.89	0.42	0.26–0.70
Intestinal metaplasia						
Corpus intestinal metaplasia	0.96	0.54–1.70	1.00	0.98–1.04	0.80	0.34–1.89
Antral intestinal metaplasia	0.84	0.44–1.59	0.98	0.48–2.02	0.54	0.18–1.59
Any intestinal metaplasia	1.12	0.72–1.73	1.25	0.76–2.05	0.86	0.44–1.66

BE, Barrett's esophagus; CI, confidence interval; *N*, number of subjects; OR, odds ratio.

The estimates are calculated using separate logistic models comparing BE cases to screening colonoscopy controls (*N*=439). All models include (control for) age and non-Hispanic white race, and screening colonoscopy controls were used.

Table 4

Estimates of the effect of *Helicobacter pylori* on BE after controlling for putative intermediates[a,b]

Factors adjusted	OR	95% CI
Age & race only[b]	0.55	0.35–0.84
Additional adjustment		
Any corpus atrophy	0.56	0.35–0.89
Any antral atrophy	0.53	0.33–0.86
Any atrophy	0.54	0.35–0.84
Any corpus intestinal metaplasia	0.39	0.19–0.82
Any antral intestinal metaplasia	0.42	0.20–0.86
Any intestinal metaplasia	0.38	0.18–0.80
Any corpus gastritis	0.79	0.47–1.31
Gastritis exclusively in the antrum	0.55	0.35–0.85
Any antral gastritis	0.75	0.43–1.32
Any gastritis[c]	0.75	0.45–1.23
GERD symptoms ≥1 week	0.54	0.35–0.84
GERD duration	0.54	0.33–0.88

BE, Barrett's esophagus; CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio.

Estimates were calculated from logistic regression models.

[a] All models include (control for) age and white race.

[b] Non-Hispanic whites.

[c] Any gastritis is defined by the presence of at least grade 2 neutrophils or mononuclear cells in at least one gastric biopsy site or grade 1 neutrophils or mononuclear cells in at least two sites.

Table 5

Assessment of effect modification

Effect modifier	OR 95% CI among those with the effect modifier(s)[a]	OR 95% CI among those without the effect modifier(s)[a]	*P* value likelihood ratio test[b]
PPI or H2RA use at least weekly	0.56 (0.27, 1.14)	0.90 (0.49, 1.66)	0.29
Corpus atrophy	0.46 (0.18, 1.18)	0.59 (0.35, 1.01)	0.83
Corpus gastritis	0.88 (0.51, 1.51)	0.33 (0.07, 1.64)	0.18
Corpus gastritis or corpus atrophy	0.82 (0.48, 1.41)	0.33 (0.07, 1.64)	0.21
PPI, H2RA, or corpus atrophy	0.28 (0.15, 0.50)	1.32 (0.66, 2.63)	0.0006
PPI, H2RA, or corpus gastritis	0.37 (0.23, 0.58)	0.95 (0.10, 9.0)	0.45
Any of the above factors	0.37 (0.23, 0.59)	0.97 (0.10, 9.1)	0.45

BE, Barrett's esophagus; CI, confidence interval; H2RA, H2 receptor antagonist; PPI, proton pump inhibitor.

[a] OR for the association between *H. pylori* infection and BE controlling for age and non-Hispanic White race.

[b] Likelihood ratio test for effect modification using the nested approach.