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Association between *Helicobacter pylori* and Barrett's Esophagus, Erosive Esophagitis, and Gastroesophageal Reflux Symptoms

Joel H. Rubenstein[1,2], **John M. Inadomi**[3], **James Scheiman**[2], **Philip Schoenfeld**[1,2], **Henry Appelman**[4], **Min Zhang**[2], **Val Metko**[2], and **John Y. Kao**[2]

[1]Center for Clinical Management Research, Ann Arbor Veterans Affairs Medical Center, Ann Arbor, MI

[2]Division of Gastroenterology, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI

[3]Division of Gastroenterology, Department of Internal Medicine, University of Washington Medical School, Seattle, WA

[4]Department of Pathology, University of Michigan Medical School, Ann Arbor, MI

Abstract

Background & Aims—Infection with *Helicobacter pylori*, particularly the cagA+ strain is believed to protect against Barrett's esophagus, but it is not clear if it protects against gastroesophageal reflux disease (GERD). We aimed to determine whether *H pylori* infection is associated with GERD symptoms, erosive esophagitis, and Barrett's esophagus within the same cohort.

Methods—We analyzed data from a case-control study 533 men (50–79 y old) who underwent colorectal cancer screening at 2 tertiary medical centers in Michigan between 2008 and 2011 and were also recruited to undergo upper endoscopy. We assessed 80 additional men found to have Barrett's esophagus during clinically indicated upper endoscopy examinations. Logistic regression was used to estimate the associations between serum antibodies against *H pylori* or cagA and GERD symptoms, esophagitis, and Barrett's esophagus, compared to randomly selected men undergoing colorectal cancer screenees (n=177).

Correspondence: Joel H. Rubenstein, MD, MS, VA Medical Center 111-D, 2215 Fuller Road, Ann Arbor, MI 48105, Phone: 734-845-5865, Fax: 734-845-3237, jhr@umich.edu.

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JS - study concept and design, acquisition of data, analysis and interpretation of data, critical revision of manuscript.
PS - study concept and design, acquisition of data, analysis and interpretation of data, critical revision of manuscript.
HA - study concept and design, acquisition of data, analysis and interpretation of data, critical revision of manuscript.
MZ - acquisition of data, analysis and interpretation of data, critical revision of manuscript.
VM - acquisition of data, analysis and interpretation of data, critical revision of manuscript.
JYK - study concept and design, acquisition of data, analysis and interpretation of data, critical revision of manuscript.

Results—*H pylori* infection was inversely associated with Barrett's esophagus (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.29 –0.97) - particularly the cagA+ strain (OR, 0.36; 95% CI, 0.14–0.90). There was a trend toward an inverse association with erosive esophagitis (*H pylori* OR, 0.63; 95% CI, 0.37–1.08 and cagA+ OR, 0.47; 95% CI, 0.21–1.03). However, GERD symptoms were not associated with *H pylori* infection (OR, 0.948; 95% CI, 0.548–1.64 and cagA+ OR, 0.967; 95% CI, 0.461–2.03).

Conclusions—Based on a case-control study, infection with *H pylori*, particularly the cagA+ strain, is inversely associated with Barrett's esophagus. We observed a trend toward an inverse association with esophagitis, but not with GERD symptoms.

Keywords

Newly Diagnosed Barrett's Esophagus Study; bacteria; stomach; BE

INTRODUCTION

In the mid-1990s, there were initial reports of patients developing either symptoms of gastroesophageal reflux disease (GERD) or endoscopic evidence of esophagitis following eradication of *Helicobacter pylori*.[1, 2] Since some patients with *H pylori* infection develop corpus atrophy with an associated decrease in gastric acid secretion, *H pylori* infection might protect against GERD and hence the development of Barrett's esophagus and esophageal adenocarcinoma. Such a protective role might explain the opposing trends in prevalence of *H pylori* infection and incidence of esophageal adenocarcinoma in Western societies. Indeed, multiple studies have demonstrated an inverse association between *H pylori* infection and the risk of esophageal adenocarcinoma or Barrett's esophagus, particularly infection with the cytotoxin-associated gene A (cagA+) strain which is more commonly associated with corpus-predominant- or pan-gastritis.[3, 4]

Despite the body of evidence supporting an inverse association between *H pylori* infection and Barrett's esophagus or esophageal adenocarcinoma, the mechanism of that association is in doubt. The initial reports of GERD symptoms or esophagitis following eradication of *H pylori* have largely not been supported by subsequent studies.[5] Furthermore, a meta-analysis of the association between *H pylori* infection and GERD found heterogeneous results, with much stronger negative effects in the Far East than in North America, and equivocal results in Europe.[6] In addition, the studies estimating the effect of *H pylori* on GERD have had a number of important limitations. Almost all of the studies were prone to bias by selection effects; only 2 studies in Western populations have used control groups not undergoing clinical evaluation for signs or symptoms of foregut disease, and neither found an inverse association between *H pylori* infection and esophagitis.[6–8] Furthermore, almost all prior studies have defined GERD on the basis of endoscopic esophagitis, and yet the majority of patients with GERD symptoms do not have erosive esophagitis. We sought to address some of these shortcomings by conducting a study examining the relationship of *H pylori* and cagA with GERD symptoms, erosive esophagitis, and Barrett's esophagus within the same study population. We hypothesized that *H pylori* infection, particularly the cagA+ strain, would be inversely associated with all 3 outcomes.

METHODS

Study Design

We conducted a case-control study as a secondary analysis of the Newly Diagnosed Barrett's Esophagus Study. [9, 10] 3 non-mutually exclusive case groups were Barrett's esophagus, erosive esophagitis, and symptomatic GERD, and controls were randomly

selected colorectal cancer screenees without any of those 3 conditions. The study enrolled male colorectal cancer (CRC) screenees, aged 50–79, presenting for colonoscopy at the University of Michigan East Ann Arbor Medical Procedure Center (UM-MPC) or the Ann Arbor Veterans Affairs Medical Center (AAVAMC) and recruited to undergo upper endoscopy. The UM Health System provides roughly 1.9 million outpatient visits annually. The UM-MPC is a satellite outpatient facility that serves primarily residents of Washtenaw County, Michigan and to a lesser extent surrounding counties, providing roughly 5,800 colonoscopies annually. Nearly 57,000 veterans residing in the Lower Peninsula of Michigan, excluding the Metropolitan Detroit area, as well as in Northwest Ohio and Northeast Indiana utilize the AAVAMC annually with roughly 600,000 outpatients visits, 3,500 colonoscopies, and 1,500 upper endoscopies. We enrolled the CRC screenees regardless of symptoms of GERD, subsequently classifying them on the basis of GERD symptoms, erosive esophagitis and Barrett's esophagus. Exclusion criteria were female sex; age < 50 or ≥80; prior history of an upper endoscopy, Barrett's esophagus, or esophagectomy; diagnostic indication for the colonoscopy; inflammatory bowel disease; known ascites or esophageal varices; cancer within the prior 5 years with the exception of non-melanoma skin cancer; significant coagulopathy; inpatient status; or inability to comprehend or cooperate with the study. Women were excluded due to the low expected prevalence of Barrett's esophagus, which would have made the study unfeasible within budgetary constraints. In addition, we recruited consecutive men aged 50–79 who had recently been diagnosed for the first time with Barrett's esophagus by a clinically indicated upper endoscopy at either the UM or AAVAMC in order to increase the precision of the effect estimates for Barrett's esophagus. The study was approved by the Institutional Review Boards of the University of Michigan and the Ann Arbor Veterans Affairs Medical Center. All authors had access to the study data and reviewed and approved the final manuscript.

After informed consent was obtained, patients had their weight, height, waist circumference, and hip circumference measured using techniques previously described.[9, 10] CRC screenees answered questions regarding GERD symptoms and medication use prior to undergoing endoscopy administered by the research staff, using questions reported previously.[9] It queried whether patients had used proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs). If patients had used these medications, it separately queried the typical frequency of heartburn or regurgitation symptoms while taking such medications and the typical frequency of symptoms when not taking such medications. If patients had not used such medications, then it only queried the typical frequency of symptoms. For the purpose of the primary analysis, patients were classified as having symptomatic GERD if they reported heartburn or regurgitation at least weekly while not taking PPIs or H2RAs (including those with or without prior use of these medications). The questionnaire used was not formally validated. For approximately the last quarter of study participants, we also administered the previously validated Mayo Clinic Gastroesophageal Reflux Questionnaire (GERQ).[11, 12] The GERQ queries symptoms during the preceding year and was developed before the wide-spread use of PPIs. It does not distinguish between symptoms while taking or not taking acid-reducing medications. The GERQ could therefore misclassify patients who have GERD well-controlled by PPI as non-GERD controls. Concordance between weekly GERD using our questionnaire and GERD symptoms meeting the Montreal definition of GERD by the GERQ (mild heartburn or regurgitation at least several days a week or at least moderate symptoms occurring at least once a week) was found in 82% of the 204 subjects completing both.[13] Among subjects not taking acid-reducing medications, there was 88% concordance.

CRC screenees first underwent colonoscopy, followed by the upper endoscopy. The distal esophagus and gastroesophageal junction were inspected both with white light and with narrow band imaging. If Barrett's esophagus was suspected by the endoscopist, biopsies

were obtained in 4 quadrants every 2cm in addition to biopsies of any visible irregularities for review by an expert pathologist (HA). Barrett's esophagus was defined as endoscopic suspicion of columnar mucosa proximal to the gastroesophageal junction with pathology finding of specialized intestinal metaplasia. Patients were classified as having esophagitis by the Los Angeles Classification scheme.[14] If Class C or D esophagitis was found, patients were instructed to repeat the endoscopy while taking a PPI, and Barrett's esophagus status was determined from the repeat endoscopy. Gastric biopsies were not routinely obtained. Non-erosive reflux symptoms were defined by subjects who were not taking any acid reducing medications at the time of the endoscopy (PPIs or H2RAs) who reported at least weekly symptoms of GERD and had a normal endoscopy without erosive esophagitis or Barrett's esophagus. Patients with Barrett's esophagus identified on a clinically indicated upper endoscopy fulfilled the same criteria for diagnosis of Barrett's esophagus as those identified among the CRC screenees. Patients self-administered a questionnaire including queries regarding tobacco use, education, and income.

Assays

Blood samples were drawn from all subjects into serum separator tubes, and serum was stored in 1mL aliquots at −80°C until the time of assay. Blood from all 150 cases of Barrett's esophagus were assayed for *H pylori*. 300 CRC screenees without Barrett's esophagus were randomly selected for assay using a random number generator in SAS 9.1 (SAS Institute, Cary, NC). In addition, available blood from all remaining CRC screenees with at least weekly GERD symptoms before use of anti-secretory medications or with erosive esophagitis regardless of anti-secretory medication use were assayed for *H pylori.* In total, blood was assayed from 613 subjects, including 150 cases of Barrett's esophagus, 153 with weekly GERD symptoms, and 222 with erosive esophagitis; the conditions are not mutually exclusive, and some subjects were included in more than 1 outcome group. Blood from 177 controls without any of the 3 conditions were assayed. IgG against *H pylori* was detected using *H pylori* IgG Enzyme Immunoassay Test Kit (Diamedix Corporation, Miami, Florida). According to the manufacturer's directions, if the result for a sample was found to be equivocal, the assay was run a second time. If still equivocal, the sample was classified for *H pylori* status based on antibodies detected against cagA. Samples that were positive or equivocal for *H pylori* were assayed for IgG against *H pylori* cagA using CagA IgG Enzyme Immunoassay Assay Well kit (Radim Diagnostics, Pomezia RM, Italy).

Statistical analysis

Data were manually entered into Microsoft Access (Microsoft, Bellevue, WA), and then imported into SAS 9.1. For descriptive characteristics associated with *H pylori* and cagA among CRC screenees, we included 328 CRC screenees in keeping with the proportion of CRC screenees overall found to have GERD symptoms, erosive esophagitis, and Barrett's esophagus. We used logistic regression to estimate effects of *H pylori* and cagA seropositivity on the presence of at least weekly GERD symptoms compared to CRC screenees without GERD symptoms, erosive esophagitis, or Barrett's esophagus, adjusting for age, waist-to-hip ratio, smoking status (ever vs. never), education (≤ vs. > high school), and race (non-Hispanic white vs. other). We fitted similar logistic regression models for the effects on erosive esophagitis, and on Barrett's esophagus, each compared to CRC screenees without any of the 3 conditions. Because the 3 conditions are not mutually exclusive, some individuals were used as outcomes in more than one model. We also fitted logistic regression models to estimate the effects of waist circumference, smoking, hiatal hernia, and Barrett's esophagus on the presence of GERD symptoms, and among patients not taking anti-secretory medications the effect of esophagitis on the presence of GERD symptoms. Finally, we fitted logistic regression models for the effects of erosive esophagitis and for Barrett's esophagus compared to men with non-erosive reflux symptoms.

RESULTS

822 male CRC screenees underwent upper endoscopy, and 328 were randomly selected for descriptive analysis of assays. 73 (22.3%) of those were found to have antibodies against *H pylori*, and 6 (1.8%) were equivocal for *H pylori* on 2 assays. Of those positive for *H pylori*, 36 (49.3%) were found to have antibodies against cagA; none of those who were equivocal for *H pylori* were found to have antibodies against cagA. 1 randomly selected CRC screenee was positive for *H pylori* but had inadequate sample for assaying against cagA. CRC screenees seropositive against *H pylori* were more likely than those seronegative to be smokers and had less education and income (Table 1).

225 CRC screenees (27.4%) were found to have esophagitis on upper endoscopy, 222 of whom had serum available for assaying. Compared to 177 randomly selected CRC screenees without any of the 3 outcomes, esophagitis was inversely associated with *H pylori* seropositivity, particularly with cagA seropositivity (Table 2). 70 CRC screenees (8.5%) were found to have Barrett's esophagus on upper endoscopy. In addition, 80 men who had been diagnosed recently for the first time with Barrett's esophagus by a clinically indicated upper endoscopy were enrolled. One patient with Barrett's esophagus was positive for *H pylori* but had inadequate sample for assaying against cagA. Compared to CRC screenees without any of the 3 outcomes, subjects with Barrett's esophagus were 50% less likely to have antibodies against *H pylori* (Table 2). Compared to CRC screenees without any of the 3 outcomes, subjects with Barrett's esophagus were approximately 70% less likely to have antibodies against cagA (Table 2).

155 CRC screenees (19.2%) reported GERD symptoms on at least weekly basis while not taking acid reducing medications, 153 of whom had serum available for assaying. We did not find any evidence of an association between *H pylori* or cagA seropositivity with GERD symptoms (Table 2). We considered that the absence of a significant association of *H pylori* with GERD symptoms might be due to inaccurate symptom-based classification of GERD status. We therefore examined the effects of factors known to be associated with GERD among CRC screenees. Patients with at least weekly GERD symptoms had greater abdominal girth (OR 3rd tertile vs. 1st tertile waist circumference = 1.75; 95% CI = 1.14, 2.68), smoked more (OR ≥ 35 pack-years vs. never smoker = 1.74; 95% CI = 1.14, 2.64), and were more likely to have a hiatal hernia (OR = 1.95; 95% CI = 1.21, 3.14), or Barrett's esophagus (OR = 2.41; 95% CI = 1.42, 4.08). Among CRC screenees not using anti-secretory medications, GERD symptoms were also associated with the endoscopic finding of esophagitis (OR = 1.87; 95% CI = 1.11, 3.14). Finally, we also examined whether any prior history of chronic GERD symptoms (defined by at least 3 months of symptoms, regardless of frequency) was associated with *H pylori*, finding no evidence for such association (*H pylori* adjusted OR = 1.13, 95% CI = 0.653, 1.96; cagA+ adjusted OR = 1.68, 95% CI = 0.791, 3.57).

Finally, we directly compared the odds of *H pylori* and cagA seropositivity between erosive esophagitis or Barrett's esophagus to men with non-erosive reflux symptoms. There were 36 patients with non-erosive reflux symptoms, defined as men with ≥weekly GERD symptoms who were not taking anti-secretory medications when they underwent endoscopy, and were found to not have erosive esophagitis or Barrett's esophagus. Compared to those men with non-erosive reflux symptoms, those with erosive esophagitis were less likely to have antibodies against *H pylori* and to cagA (Table 3). Similar results were found comparing Barrett's esophagus to non-erosive reflux symptoms.

DISCUSSION

We re-demonstrated a strong negative association between Barrett's esophagus or erosive esophagitis and *H pylori*, particularly the cagA+ strain. However, contrary to the prevailing hypothesis explaining that association, we were unable to detect a negative association between *H pylori* and GERD symptoms. This study adds to the mounting data against the hypothesis that *H pylori* infection protects against Barrett's esophagus by inhibiting GERD. Despite the initial reports to the contrary, a meta-analysis revealed that eradication of *H pylori* generally does not promote GERD.[5] Furthermore, while *H pylori* infection might prevent GERD in Asian populations, the data is less convincing for European or North American populations.[6] This may be because *H pylori* infections in Asians tend to be corpus-predominant, and the infections in Westerners tend to be antral-predominant.[15] In corpus-predominant *H pylori* infection, gastric acid output is diminished.[16] In contrast, in antral-predominant *H pylori* infection, the negative feedback of gastric acid on gastrin release is disturbed, leading to elevated gastrin and elevated gastric acid output from the corpus.[17]

If not by reducing GERD, then the mechanism of *H pylori*'s negative association with Barrett's esophagus might fall into one of three main categories: direct effects, indirect effects, or confounding effects. For example, there might be a direct systemic effect of *H pylori* DNA in down-regulating type 1 interferon and interleukin-12 responses to inflammatory stimuli.[18, 19] Similarly *H pylori* DNA in refluxate might directly down-regulate those responses locally in esophageal mucosa. Alternatively, *H pylori* might have indirect effects mediated through diminished gastric production of leptin or ghrelin.[20–22] Finally, the negative association with *H pylori* might be confounded by factors that might both predispose to Barrett's esophagus and protect against infection with *H pylori*, such as polymorphisms in IL-12p70 genes regulating cytokine cascades or alterations in the esophageal and gastric microbiota related to prior antibiotics, diet and/or hygiene.[23–25] Each of these hypotheses deserves further study.

Our study had a few notable limitations. Most importantly, it is possible that classification errors for GERD status biased the estimated associations with *H pylori* toward the null. GERD symptoms were based on a questionnaire that has shown good concordance with another validated GERD questionnaire, but the one used was not fully validated itself.[9] However, patients with GERD symptoms detected by our questionnaire demonstrated the expected associations with abdominal obesity, tobacco use, erosive esophagitis, and Barrett's esophagus. Additionally, given the imprecise estimates (wide confidence intervals) of the effects of *H pylori* and cagA seropositivity on the odds of GERD symptoms, we cannot entirely exclude either a protective role or a promoting role for that outcome. There were however strong, statistically significant inverse associations of *H pylori* and cagA+ with erosive esophagitis and with Barrett's esophagus compared to men with non-erosive reflux symptoms, suggesting that *H pylori* may protect against development of esophagitis and Barrett's esophagus among patients with GERD. In addition, there might have been classification errors for esophagitis since we did not routinely obtain biopsies for histology, instead relying on endoscopic appearance as classified by the Los Angeles classification scheme. Nonetheless, classification errors would be more likely to bias the estimated effect for erosive esophagitis toward the null, and unlikely to bias the estimate in favor of a strong protective effect. It seems unlikely therefore that such classification error would explain the result. Finally, our effect estimates may have been biased toward the null by classification errors for *H pylori* or cagA statuses as we only used serology and did not confirm the presence of the bacteria or the location and extent of gastritis and atrophy by histology of gastric biopsies. In any case, if *H pylori* prevents Barrett's esophagus by inhibiting GERD,

then classification errors for *H pylori* status would not be expected to differentially bias the estimates of effects on GERD symptoms versus Barrett's esophagus.

Our study also has a number of notable strengths. Our unique design allowed us to simultaneously estimate the effects of *H pylori* on all 3 outcomes of GERD symptoms, esophagitis, and Barrett's esophagus within the same cohort. While meta-analyses have suggested similar findings in Western populations as in our study, those summary estimates of effects on esophagitis and Barrett's esophagus are not directly comparable due to differences in study designs across studies and heterogeneity of results.[4, 6]

In summary, our findings suggest a strong inverse association of *H pylori* with erosive esophagitis and Barrett's esophagus, particularly in the cagA+ strain, but we were not able to detect an inverse association with GERD symptoms.

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Abbreviations

BE	Barrett's esophagus
BMI	body mass index
cagA	cytotoxin-associated gene A
CI	confidence interval
CRC	colorectal cancer
EE	erosive esophagitis
GERD	gastroesophageal reflux disease
OR	odds ratio
SD	standard deviation
WHR	waist-to-hip ratio

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Table 1

Baseline Factors by *H pylori* and cagA Seroprevalence among Randomly Selected Colorectal Cancer Screenees

	***H pylori* − (n = 255)**	***H pylori* +**		
		cagA − or + (n = 73)[b]	**cagA − (n = 36)**	**cagA + (n = 36)**
Age (years)[a]	58.9 (6.5)	59.5 (6.4)	58.7 (5.5)	60.4 (7.1)
Body mass index (kg/m^2)[a]	29.9 (5.4)	30.5 (6.1)	30.8 (6.2)	29.9 (6.1)
Waist-to-hip ratio[a]	1.001 (0.059)	1.008 (0.054)	1.008 (0.051)	1.008 (0.058)
Smoking status (current or former)	67%	80%	89%	71%
Education (≤ high school)	17%	37%	34%	41%
Income (< $40,000 per year)	33%	52%	50%	55%
non-Hispanic White	93%	86%	83%	90%
Enrollment site (VA)	41%	52%	61%	44%

[a] Data presented as mean (standard deviation)

VA: Ann Arbor Veterans Affairs Medical Center

[b] 1 patient was positive for *H pylori*, but had inadequate sample for assaying cagA.

Table 2

Associations of *H pylori* and cagA Seroprevalence with Symptoms of Gastroesophageal Reflux, Erosive Esophagitis, or Barrett's Esophagus.

***H pylori* / cagA Status**	**# No GERD, EE, or BE[b]**	**GERD**			**Erosive Esophagitis**			**Barrett's Esophagus**		
		# GERD	**Crude OR (95% CI)**	**Adjusted OR (95% CI)[a]**	**# EE**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**	**# BE[b]**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
H pylori −	131	115	1 (Reference)	1 (Reference)	182	1 (Reference)	1 (Reference)	125	1 (Reference)	1 (Reference)
H pylori +	46	38	0.94 (0.57, 1.55)	0.95 (0.55, 1.64)	40	0.63 (0.39, 1.01)	0.63 (0.37, 1.08)	25	0.57 (0.33, 0.98)	0.53 (0.29, 0.97)
H pylori +, cagA −	22	20	1.04 (0.54, 1.99)	0.93 (0.46, 1.88)	25	0.82 (0.44, 1.51)	0.78 (0.40, 1.54)	16	0.76 (0.38, 1.52)	0.64 (0.30, 1.36)
H pylori +, cagA +	23	18	0.89 (0.46, 1.74)	0.97 (0.46, 2.03)	15	0.47 (0.24, 0.93)	0.47 (0.21, 1.03)	8	0.365 (0.16, 0.85)	0.36 (0.14, 0.90)

[a] Adjusted for age, waist-to-hip ratio, smoking status, education, and race.

BE: Barrett's esophagus, CI: confidence interval, GERD: gastroesophageal reflux disease, EE: erosive esophagitis, OR: odds ratio

[b] 1 normal patient and 1 with BE was positive for *H pylori*, but had inadequate sample for assaying cagA.

Table 3

Associations of *H pylori* and cagA Seroprevalence with Erosive Esophagitis or Barrett's Esophagus Compared to CRC Screenees with Non-Erosive Reflux Symptoms.

***H pylori* / cagA**	**# NER Symptoms**	**Erosive Esophagitis**			**Barrett's Esophagus**		
		# EE	**Crude OR (95% CI)**	**Adjusted OR (95% CI)[a]**	**# BE**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)[a]**
H pylori −	25	182	1 (Reference)	1 (Reference)	125	1 (Reference)	1 (Reference)
H pylori +	11	40	0.50 (0.23, 1.10)	0.41 (0.18, 0.968)	25	0.46 (0.20, 1.04)	0.29 (0.11, 0.74)
H pylori +, cagA −	5	25	0.69 (0.24, 1.96)	0.60 (0.20, 1.84)	16	0.64 (0.22, 1.91)	0.49 (0.15, 1.60)
H pylori +, cagA +	6	15	0.34 (0.12, 0.967)	0.25 (0.08, 0.80)	8	0.27 (0.09, 0.84)	0.13 (0.03, 0.48)

[a] Adjusted for age, waist-to-hip ratio, smoking status, education, and race.

BE: Barrett's esophagus, CI: confidence interval, EE: erosive esophagitis, NERD: non-erosive reflux , OR: odds ratio

[b] 1 patient with BE was positive for *H pylori*, but had inadequate sample for assaying cagA.