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

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BACKGROUND & AIMS: **Infection with *Helicobacter pylori*, particularly the cytotoxin-associated gene A (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 of 533 men (ages, 50–79 y) who underwent colorectal cancer screening at 2 tertiary medical centers in Michigan between 2008 and 2011 and who also were 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 with randomly selected men undergoing colorectal cancer screens (n = 177).**

RESULTS: ***H pylori* infection was associated inversely 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 associated inversely 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.

In the mid-1990s, there were initial reports of patients developing either symptoms of gastroesophageal reflux disease (GERD) or endoscopic evidence of esophagitis after eradication of *Helicobacter pylori*.[1,2] Because 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 shown 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 associated more commonly with corpus-predominant gastritis 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

Abbreviations used in this paper: AAVAMC, Ann Arbor Veterans Affairs Medical Center; cagA, cytotoxin-associated gene A; CI, confidence interval; CRC, colorectal cancer; GERD, gastroesophageal reflux disease; GERQ, Gastroesophageal Reflux Questionnaire; H2RA, histamine-2–receptor antagonist; IgG, immunoglobulin G; OR, odds ratio; PPI, proton pump inhibitor.

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GERD symptoms or esophagitis after 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 used control groups that were not undergoing clinical evaluation for signs or symptoms of foregut disease, and neither study 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 associated inversely 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] Three nonmutually 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 to 79, presenting for colonoscopy at the University of Michigan East Ann Arbor Medical Procedure Center or the Ann Arbor Veterans Affairs Medical Center (AAVAMC) and recruited to undergo upper endoscopy. The University of Michigan Health System provides roughly 1.9 million outpatient visits annually. The University of Michigan East Ann Arbor Medical Procedure Center is a satellite outpatient facility that serves primarily residents of Washtenaw County, Michigan, and to a lesser extent surrounding counties, providing roughly 5800 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, use the AAVAMC annually with roughly 600,000 outpatient visits, 3500 colonoscopies, and 1500 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 younger than 50 or age 80 and older; 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 nonmelanoma skin cancer; significant coagulopathy; inpatient status; or inability to comprehend or cooperate with the study. Women were excluded because of 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 to 79 who recently were diagnosed for the first time with Barrett's esophagus by a clinically indicated upper endoscopy at either the University of Michigan or the AAVAMC 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 AAVAMC. 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 before undergoing endoscopy administered by the research staff, using questions reported previously.[9] The questionnaire queried whether patients had used proton pump inhibitors (PPIs) or histamine-2–receptor antagonists (H2RAs). If patients had used these medications, the questionnaire 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 widespread use of PPIs. It does not distinguish between symptoms while taking or not taking acid-reducing medications. The GERQ therefore could misclassify patients who have GERD that is well controlled by a 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 questionnaires.[13] Among subjects not taking acid-reducing medications, there was 88% concordance.