H. pylori May Protect Against Esophageal Cancer

BY DENISE NAPOLI

FROM GASTROENTEROLOGY

Patients with esophageal adenocarcinoma and esophagogastric junction adenocarcinoma were significantly less likely than population controls to have evidence of past *Helicobacter pylori* infection, Dr. David C. Whiteman and his colleagues reported.

The association persisted independently of known esophageal cancer risk factors, such as reflux and smoking, and also was independent of genetic factors, including polymorphisms in genes coding for interleukin-1B and tumor necrosis factor–alpha.

The findings add to a growing body of evidence suggesting that *H. pylori* might somehow be protective against esophageal cancers, even as it increases the risk of gastric cancer.

Dr. Whiteman, head of the Cancer Control Laboratory at the Queensland (Australia) Institute of Medical Research looked at 794 Australian patients aged 18-79 years with a primary invasive cancer of the esophagus or esophagogastric junction.

Overall, 269 patients had esophageal adenocarcinoma, 307 had esophagogastric junction adenocarcinoma, and 218 had esophageal squamous cell carcinoma.

The 1,355 controls were randomly selected from the Australian Electoral Roll and were roughly matched to the patients by age, sex, and state of residence.

"Patients with [esophageal adenocarcinoma, or EAC] and [esophagogastric junction adenocarcinomas, or EGJAC] were significantly less likely than were controls to have antibodies to *H. pylori*," wrote Dr. Whiteman (Gastroenterology July [doi: 10.1053/j.gastro.2010.04.009]).

Among the EAC patients, the odds ratio of being seropositive was 0.44 (95% confidence interval, 0.29-0.67) after researchers adjusted for age, sex, smoking history, education, and several other environmental factors.

In the EGJAC population, the OR was 0.40 (95% CI, 0.27-0.59).

There was no association between *H. pylori* and esophageal squamous cell carcinoma (OR 1.08, 95% CI 0.74-1.57), they reported.

Dr. Whiteman and his colleagues also looked to see whether esophageal cancer patients shared any common mutations in the genes coding for IL-1B and TNF-alpha.

"IL-1B is among the most potent inhibitors of gastric acid yet identified," they wrote, and "a recent meta-analysis concluded that the TNF-A -308AA genotype is associated with a moderately increased risk of gastric cancer" (Br. J. Cancer 2008;98:1443-51).

However, the authors "found no evidence that the inverse associations between *H. pylori* infection and [esophageal adenocarcinomas or esophagogastric junction adenocarcinomas] were modified by the presence of polymorphisms at IL-1B-31, IL-1B-511, TNF-A 308, and TNF-A 238."

Squamous cell carcinomas also had a null association with these genotypes, they reported.

Therefore, Dr. Whiteman and his colleagues asked, "Is the inverse relationship between *H. pylori* infection and EAC and EGJAC evidence of a biologically protective effect?" And if so, what is the mechanism?

"Several potential mechanisms have been proposed to explain the association, including hypoacidity subsequent to prolonged infection, dysregulation of host cytokine or immune responses, disturbances to microbial flora, and changes in the expression of locally acting hormones relating to obesity pathways (notably leptin and ghrelin)," wrote the authors.

"Each of these hypotheses is plausible, and all may indeed play a role," they commented.

As for study limitations, the authors conceded that the overall prevalence of *H. pylori* antibodies (23% among controls) was much lower than in other populations, including in the United States.

However, the "50-60% risk reductions we observed for EAC were remarkably similar to those reported in other studies," they wrote.

As to the possibility of misclassification of *H. pylori* exposure, Dr. Whiteman and his colleagues pointed out that for such an error to have occurred "would [have] required that patients with EAC and EGJAC, but not [esophageal squamous cell carcinomas], were incorrectly categorized, a highly improbable scenario." ■

VITALS

Major Finding: Patients with esophageal adenocarcinoma and esophagogastric junction adenocarcinoma were significantly less likely to have a history of *H. pylori* infection than population controls (odds ratios, 0.44 and 0.40, respectively).

Data Source: An Australian study of 269 patients with esophageal adenocarcinoma, 307 with esophagogastric junction adenocarcinoma, and 218 with esophageal squamous cell carcinoma, compared with 1,355 controls.

Disclosures: Dr. Whiteman and several of his colleagues disclosed receiving grants from the National Health and Medical Research Council of Australia. The study was supported by the Cancer Council Queensland and the National Health and Medical Research Council of Australia.

Hip Fracture Risk May Be Higher With Long-Term PPI Use

BY DENISE NAPOLI

FROM GASTROENTEROLOGY

Hip fracture patients were 30% more likely to have a long-term history of proton pump inhibitor use, compared with controls, Dr. Douglas A. Corley and his colleagues reported.

Moreover, the association was found to be stronger with higher doses of PPIs, and the link diminished after PPI discontinuation, the researchers wrote.

"These findings do not recommend against acid suppression for persons with clear indications for treatment," wrote Dr. Corley, a researcher with Kaiser Permanente Northern California (Gastroenterology July [doi: 10.1053/j.gastro.2010.03.055]). However, "they do advise appropriate vigilance in prescribing these medications to persons with defined indications and at the lowest effective dose."

Dr. Corley and his colleagues looked at 33,752 adult members of the Kaiser Permanente Northern California integrated health care delivery system who had an incident diagnosis of a hip fracture between January 1995 and September 2007. To be included in the study, patients had to have been in the Kaiser Permanente Northern California system for at least 2 years prior to their fracture. Patients who had a previous hip or femur fracture diagnosis were excluded.

Patients were roughly matched in a 4:1 ratio with demographically comparable controls, also from the Kaiser Permanente Northern California system. Controls had no history of hip fracture, and had also been in the Kaiser system for at least 2 years.

Patients were predominantly women (65.7%), 70 years of age or older (69.4%), and white (79.6%), according to the authors. Roughly 40% had received a prescription for a proton pump inhibitor while in the Kaiser Permanente Northern California system.

According to Dr. Corley, patients whose records indicated "long-term" use of PPIs (defined by the authors as greater than 2 years) had an odds ratio of having a fracture within the study period of 1.30, compared with nonusers (95% confidence interval, 1.21-1.39).

However, all of the increased risk for fracture was present only in patients who had at least one other risk factor for fracture, such as smoking, dementia, arthritis, or visual impairment. Indeed, among patients with none of these risk factors, the odds ratio for fracture among PPI users was 0.66 (95% CI, 0.38-1.12).

The researchers also found a trend toward increased fracture risk among subjects taking higher daily doses of PPIs. For example, among patients taking an average of 0.01-0.74 pills/day, for a duration between 2 and 3.9 years, the OR for a fracture, compared with nonusers, was 1.23 (95% CI, 1.08-1.39); among users taking 0.75-1.49 pills/day, for the same duration of time, the OR was 1.43 (95% CI, 1.28-1.60), and for more than 1.49 pills/day the OR was 1.41 (95% CI, 1.21-1.64).

Despite the association with PPI dosage, there was no link between duration of PPI use and fracture risk.

The researchers also found that "the strength of the association between PPI use and hip fracture was greatest among current users and diminished after discontinuation of PPI use." For example, while the OR for current users was 1.30 (95% CI, 1.21-1.41), it was 1.24 for patients whose most recent prescription was 1.0-1.9 years before the index date (95% CI, 0.90-1.72), and dropped to 1.09 for patients whose last PPI prescription was 2.0-2.9 years before the index date (95% CI, 0.64-1.85).

Dr. Corley proposed several mechanisms by which acid inhibition could influence fracture risk. For one, he said, acid inhibition could directly influence calcium absorption: He pointed to a small, randomized trial in which omeprazole decreased the absorption of radiolabeled calcium pills by 61%, compared with placebo (Am. J. Med. 2005;118:778-81). "Second," he wrote, "acid inhibition may induce hyperparathyroidism, which directly decreases bone mineral density, through hypergastrinemia, although this is controversial." Finally, he suggested that fracture risk may be mediated by interference by PPIs with bone remodeling. However, he added, "none of these mechanisms are proven." ■

VITALS

Major Finding: Among patients taking proton pump inhibitors for at least 2 years, the risk of having a hip fracture was increased by 30%, but only when at least one other fracture risk factor (smoking, dementia, arthritis, visual impairment) was present. Among PPI users with none of these other risk factors, the odds ratio for fracture was 0.66.

Data Source: A nested case-control study using data from an integrated health services organization, including 33,752 cases and 130,471 controls, published in the July issue of the journal Gastroenterology.

Disclosures: Dr. Corley disclosed receiving research funding, unrelated to this study, from Wyeth Pharmaceuticals, which makes a proton pump inhibitor. The remaining authors disclose no conflicts of interest. The study was funded by Kaiser Permanente and a grant from the U.S. National Institutes of Health.