EDITORIAL

Helicobacter pylori Treatment for Gastric Cancer Prevention

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Gastric cancer has become a potentially preventable disease through eradication of *Helicobacter pylori*. However, issues that are associated with "screen and treat" strategies — their effectiveness, proper selection of populations to target, and cost–benefit considerations — continue to interfere with the application of such strategies in regular practice.

A major uncertainty relates to the most effective timing for the implementation of a screen-and-treat program. One factor influencing this uncertainty is whether *H. pylori* eradication is effective at stopping the carcinogenic process in patients with severe chronic atrophic gastritis, an advanced precursor lesion to gastric cancer.[1]

In this issue of the *Journal*, Choi et al.[2] report the results of their randomized, placebo-controlled trial, in which at a median follow-up of 5.9 years, *H. pylori* eradication was effective in the prevention of metachronous gastric cancer (hazard ratio, 0.50) after selective endoscopic removal of early-stage disease. (In this trial, a gastric cancer was defined as "metachronous" if it was detected on endoscopy at the 1-year follow-up or later.) In this endoscopic procedure, removal of early gastric cancer or high-grade adenoma leaves the stomach largely conserved but with the atrophic gastric mucosa remaining in a preneoplastic "alarm state." It is a striking finding that *H. pylori* eradication may still be effective at this stage, since such therapy decreased the development of gastric cancer by 50% in this trial.

From a global perspective, gastric cancer ranks third among cancer-related mortality despite a substantial decrease in incidence over the past decades and variable incidence in different geographical regions.[3] The economic burden on health systems is high, and the disease is difficult to treat because diagnosis is usually made in an advanced stage. The clinical course is characterized by a high symptom burden and an expected median 5-year survival of less than 30% in the Western world. No institutionalized screening programs exist for gastric cancer prevention in Western countries.

The picture is different in East Asia, where approximately two thirds of all gastric cancers worldwide are diagnosed. Screening strategies that are aimed at the detection of gastric cancer at an early and more curable stage have led to a significant reduction in mortality from the disease.[4]

The most relevant new target in gastric cancer prevention is *H. pylori* infection. Unequivocal evidence from epidemiologic, basic, and clinical research has identified *H. pylori* as a primary factor in the multifactorial pathogenesis of gastric cancer.[5] Approximately 90% of noncardia gastric cancers are attributable to *H. pylori* infection, and eradication therapy has been shown to be effective in the prevention of primary gastric cancer in several well-conducted clinical trials.[6] In a community with a high incidence of gastric cancer, mass eradication of *H. pylori* led to a significant reduction in the development of the disease.[7] Furthermore, the incidence of gastric cancer was lower among patients who received *H. pylori* therapy than among those who received supplementation with dietary antioxidants during 15 years of follow-up,[8] and a similar long-term beneficial effect was confirmed for *H. pylori* eradication, as compared with vitamin supplements, in preventing the progression of precancerous lesions.[9]

Will all this evidence push open the door for the universal adoption of strategies to screen for and treat *H. pylori* for gastric cancer prevention? Nearly all controlled trials to date have been carried out in East Asia. According to data from these trials, 125 persons would need to be treated to prevent one case of gastric cancer, so such a strategy is cost-effective in countries with a high incidence of the disease. The number of persons who would need to be treated would be much higher in countries with a low or intermediate incidence of gastric cancer, a factor that has been used to argue against preventive strategies in these populations. However, modeling studies that include economic considerations and additional clinical benefits beyond gastric cancer prevention (e.g., the prevention of ulcers and gastric lymphoma) suggest that *H. pylori* screen-and-treat strategies also merit consideration in communities at low or intermediate risk.[10]

With respect to the most effective timing for screen-and-treat programs, we know that *H. pylori* therapy can cure chronic active gastritis in the absence of atrophy, since the gastric mucosa is restored to normal and the risk of the development of gastric cancer is substantially reduced. Severe atrophic gastritis with or without intestinal metaplasia has been considered as the "point of no return" that marks the stage at which the elimination of *H. pylori* (if still present) may no longer arrest cancer development. This claim has been challenged by previous studies that have provided evidence of metachronous cancer prevention by *H. pylori* eradication after endoscopic resection of early gastric cancer.

The results of Choi et al. confirm and strengthen the previous findings by showing a significant improvement in atrophic gastritis in half the trial patients. The investigators did not address whether the recurrence of gastric cancer was prevented only in the patients with improvement in atrophic gastritis or if these events were not related. *H. pylori* eradication may arrest carcinogenic mechanisms directly by abolishing persistent inflammation. The beneficial effect may also be mediated by an alteration in the composition of the gastric microbiota because of improvement in the grade of gastric atrophy and a return toward normal gastric acid production.

Gastric cancer prevention can be achieved by *H. pylori* screen-and-treat strategies with selection of the most effective timing for intervention. These strategies are mandatory in populations at high risk and are established in guidelines for other persons at risk. Consideration should also be given to populations with low or intermediate risk. Such strategies should be implemented before the establishment of severe gastric atrophic changes with or without intestinal metaplasia, according to local needs and resources. The first approach to prevention should be noninvasive (i.e., serologic analysis), which can be followed by endoscopy in patients at risk. Such an approach should be encouraged in combination with screening for colorectal cancer in patients older than 50 years of age in Western societies that have a low or intermediate risk of gastric cancer.

H. pylori eradication is still effective in patients with advanced preneoplastic lesions. The intervention prevents later gastric cancer in only a subgroup of patients, so endoscopic or histologic surveillance remains mandatory. This requirement extends to all patients with severe atrophic gastritis with or without intestinal metaplasia even after successful eradication. Since the selection of eradication therapy is aimed at minimizing the development of antimicrobial resistance, bismuth-based regimens should be given preference.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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1. Rugge M, Genta RM, Di Mario F, et al. Gastric cancer as preventable disease. Clin Gastroenterol Hepatol 2017;15:1833-43.

2. Choi IJ, Kook M-C, Kim Y-I, et al. *Helicobacter pylori* therapy for the prevention of metachronous gastric cancer. N Engl J Med 2018;378:1085-95.

3. Ferlay J, Soerjomartaram I, Dikshit R et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN. Intl J Cancer 2015;136(5):E359-E386.

4. Jun JK, Choi KS, Lee HY, et al. Effectiveness of the Korean National Cancer Screening Program in reducing gastric cancer mortality. Gastroenterology 2017;152:1319-1328.e7.

5. Malfertheiner P, Link A, Selgrad M. Helicobacter pylori: perspectives and time trends. Nat Rev Gastroenterol Hepatol 2014; 11:628-38.

6. Lee YC, Chiang TH, Chou CK et al. Association between Helicobacter pylori eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology 2016;150: 1113-24.

7. Lee YC, Chen TH, Chiu HM, et al. The benefit of mass eradication of Helicobacter pylori infection: a community-based study of gastric cancer prevention. Gut 2013;62:676-82.

8. Ma JL, Zhang L, Brown LM, et al. Fifteen-year effects of

Helicobacter pylori, garlic, and vitamin treatments on gastric cancer incidence and mortality. J Natl Cancer Inst 2012;104:488-92.
9. Mera RM, Bravo LE, Camargo MC, et al. Dynamics of Helicobacter pylori infection as a determinant of progression of gastric precancerous lesions: 16-year follow-up of an eradication trial. Gut 2017 June 24 (Epub ahead of print).
10. Malfertheiner P, Megraud F, O'Morain CA et al. Management of Helicobacter pylori infection — the Maastricht V/Florence Consensus Report. Gut 2017:66:6-30.

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