Prevention of Gastric Cancer With Antibiotics: Can It Be Done Without Eradicating *Helicobacter pylori*?

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Gastric cancer is the second most common cancer in the world, and *Helicobacter pylori* infection is the single most important risk factor for gastric cancer. *H. pylori* is recognized as a class I or definite carcinogen by the World Health Organization (1), and current clinical guidelines from the United States (2), Europe (3), and Asia (4) advocate *H. pylori* eradication in people at high risk for gastric cancer. However, the efficacy of this approach is unknown, partly because it is uncertain when the cascade of neoplastic changes induced can be halted. Specifically, does *H. pylori* play an important role in the later stages of neoplastic progression? Recent evidence suggests that other elements of the gastric microbiome are also important in the development of gastric cancer, either as cofactors or as drivers of neoplasia. The article by Li et al. in this issue of the Journal presents new analyses from the Shandong Intervention Trial that shed light on a broader role for antibiotics in the prevention of gastric cancer (5).

Randomized clinical trials have shown that antibiotics targeting *H. pylori* can prevent secondary outcome measures related to gastric cancer. Among patients from a high-risk area in China with precursor lesions, 1 week of antibiotics reduced the rate of progression of intestinal metaplasia compared with placebo (9). Correa et al. randomized adults with precursor gastric lesions to antibiotics vs placebo and demonstrated that regression of metaplasia was proportional to the amount of time spent free of *H. pylori* infection (10). Furthermore, among patients who underwent endoscopic resection for early gastric cancer, treatment with 1 week of antibiotics reduced risk for metachronous gastric cancer after 3 years of follow-up (11). Finally, a large randomized trial was conducted in Changle County in Fujian Province, China, an area with a remarkably high baseline rate of gastric cancer (150 per 100,000 population) (12). Among 1630 participants with positive *H. pylori* serologies randomly assigned to 2 weeks of antibiotics vs placebo and actively followed for 7.5 years, there was no statistically significant difference in the incidence of gastric cancer. In a post hoc analysis, the investigators identified a protective effect for antibiotics among those without precursor lesions. This finding led to speculation that *H. pylori* infection may cause in patients an early “point of no return”—the development of intestinal metaplasia—after which treatment with antibiotics has minimal effect.

Well-established animal models of gastric cancer led to quite different conclusions: that gastric inflammation is initiated by *H. pylori* infection, but continuing gastric dysbiosis is required for progression to malignancy and can be largely inhibited. In C57BL/6 mice housed under normal barrier conditions, chronic infection with the Sydney strain of *H. pylori* or *Helicobacter felis* leads almost invariably to multifocal atrophic gastritis with hypochlorhydria, metaplastic changes, and gastric cancer (13). Although antibiotic eradication at 2 months was highly effective in preventing cancer, treatment deferred for 1 year and given at a dysplastic stage still reversed inflammation, restored normal architecture, and prevented gastric cancer (14). INS-GAS transgenic mice overexpress gastrin and progress rapidly to dysplasia and cancer when infected with *Helicobacter* (15). Again, although early treatment at 8 weeks completely prevented dysplasia, treatment at a late time point (22 weeks) still inhibited progression to cancer (16). These studies indicate that antibiotics are highly effective at halting progression toward gastric cancer when given early in *H. pylori* infection but remain effective in animals even when given after dysplasia is present.

Antibiotics targeting *H. pylori* have effects on other bacteria as well. The development of intestinal metaplasia after *H. pylori* infection can be accompanied by achlorhydria and a decrease in the abundance of *H. pylori*, as well as increased colonization by other bacterial species (bacterial overgrowth) (17). Recent studies have demonstrated that these other bacteria play an important role in the development of gastric neoplasia. Using gnotobiotic INS-GAS mice, Lofgren et al. determined that *H. pylori*–monoassociated mice developed gastric intraepithelial neoplasia (GIN) more slowly than *H. pylori*–infected INS-GAS mice with complex microbiota (18). Additionally, *H. pylori*–uninfected INS-GAS mice colonized with intestinal flora developed GIN more quickly than germ-free mice. In a separate set of experiments, germ-free INS-GAS mice infected with *H. pylori* did not develop GIN, but *H. pylori*–infected mice colonized with eight defined species (Altered Schaedler’s Flora) developed GIN in an otherwise germ-free environment (19). Thus, non-*H. pylori* bacteria that colonize the atrophic stomach may in fact be the critical drivers for gastric cancer progression after initial infection with *H. pylori*.

The newest results from the Shandong Trial speak to this issue. The Shandong Intervention Trial was conducted in the Linqu County of the Shandong Province, where gastric cancer accounted for 42% of all cancer deaths in the 1980s (20). The study used a factorial design to randomly assign participants to antibiotics directed against *H. pylori* (2 weeks of amoxicillin and omeprazole), vitamins, garlic, or placebo. A total of 2258 participants had positive *H. pylori* serologies and were randomly assigned in 1995 to antibiotics vs placebo. Participants who received antibiotics were retested and
retreated in 1996 (n = 382). All participants were actively followed, including with scheduled upper endoscopies, and in 2003, H. pylori infection status was determined by breath test or serology. After 7.3 years of follow-up, the study showed a non-statistically significant difference in incidence of gastric cancer of 1.7% among those who received antibiotics compared with 2.4% among those who received placebo (21). However, after 15 years of follow-up, these rates were statistically significantly different at 3.0% and 4.6%, respectively, although gastric cancer–related mortality was not statistically significantly different (22).

In their article, Li et al. expand on the 15-year follow-up findings by performing stratified analyses of gastric cancer incidence and mortality by histopathology, age, and H. pylori infection status (5). They found that antibiotics directed against H. pylori statistically significantly decreased gastric cancer incidence and mortality among participants aged 55 years or older who have been infected for longer periods and are more likely to have advanced lesions. In contrast with the trial by Wong et al. (12), antibiotic treatment statistically significantly decreased gastric cancer incidence among participants who already had intestinal metaplasia or dysplasia at the time of baseline endoscopy. Importantly, non-statistically significant decreased risks of gastric cancer were seen not only in those with successful H. pylori eradication but also among those treated and with persistent infection. The authors state that the most likely explanation for their findings is that even a short-term interruption in infection can slow the progression to cancer and that H. pylori infection promotes these later stages of carcinogenesis. Based on the animal studies summarized herein, we believe that their alternative explanation is more likely: treatment with antibiotics decreases the incidence of gastric cancer through mechanisms unrelated to H. pylori, most likely by eliminating non–H. pylori bacteria that are critical to later stages of neoplastic progression.

The latest results from the Shandong Trial are consistent with other human and animal data that H. pylori–induced gastric atrophy leads to dysbiosis that is at least partly corrected by antibiotic treatment. Once the role of specific elements of the gastric microbiome on the development of gastric cancer in humans is further elucidated, chemoprevention trials can be better designed to target gastric dysbiosis and not focus solely on H. pylori.

References


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Notes

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