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Research of the eradication of Helicobacter pylori to prevent gastric cancer

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Author contributions

Zhao-Chun Chi was responsible for reviewing academic papers in gastric cancer field and writing manuscripts.

Competing interests

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Abbreviations

H. pylori, Helicobacter pylori; GC, Gastrointestinal cancer; IL, interleukin; COX-2, cyclooxygenase 2.

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Abstract

Gastric cancer (GC) is primarily caused by Helicobacter pylori (H. pylori). Approximately 50% of Chinese people have H. pylori, and H. pylori is responsible for 90% of stomach cancer cases. Thus far, the best method of preventing the development of stomach cancer is the inhibition of H. pylori. The incidence and fatality rates of stomach cancer can be considerably reduced by population-based H. pylori eradication.

Keywords: prevention; gastric cancer; metachronous occurrence; epigenetic chemoprevention

Background

The clearance of *Helicobacter pylori* (*H. pylori*) infection can prevent the occurrence of gastric cancer (GC), which has received increasing interest and a widespread consensus. At a recent global meeting regarding *H. pylori*, it was shown that *H. pylori* eradication reduces the risk of GC among asymptomatic subjects. Additionally, *H. pylori* eradication after endoscopic resection of early GC diminishes the risk of metachronous cancer. Therefore, evidence supports the use of eradication therapy for all *H. pylori*-infected individuals. In populations at high risk for GC, mass screening for and eradication of *H. pylori* should be considered [1].

GC is the third most common cause of cancer-related death worldwide. Its normal progression includes chronic gastritis, mucosal atrophy, epithelial metaplasia, intraepithelial neoplasia, and, ultimately, invasive cancer [2]. The elimination of *H. pylori* promotes inflammatory healing and stops the progression of genetic and mucosal damage associated with *H. pylori.* Eradication treatment was used by Chiang et al [3]. To completely eradicate *H. pylori* infection, resulting in a yearly per capita reinfection rate less than 1%, and the prevalence of *H. pylori* infection decreased from 64.2% to 15.0%. Atrophic gastritis and intestinal metaplasia both became less frequent and less severe over time as well.

Impact of eliminating H. pylori on the development of gastric inflammation, intestinal metaplasia, and cancer

Previous research has attempted to clarify whether and to what extent *H. pylori* eradication in humans can reverse a series of processes in intestinal metaplasia and acute gastritis. An endoscopic analysis was performed to determine whether *H. pylori*-positive specimens had enlarged or elongated pits that were smaller, rectangular, pinhole-sized, or round and had fine, irregular blood vessel densities. This change was not observed in samples from subjects with severe gastric atrophy and intestinal metaplasia [4]. However, after *H. pylori* eradication, various studies have not always revealed histological advancements in intestinal metaplasia and gastric atrophy [5]. Contrarily, some studies have shown that eradication can effectively treat antrum or corpus digestive lesions [6]. In these studies, endoscopy revealed that positive *H. pylori* specimens showed significant morphological changes, with the initial elongated and expanded pits progressively developing into tiny, irregular, oval pits. Atrophic gastritis and intestinal metaplasia patients did not exhibit this improvement in pathological specimens [4]. Nevertheless, other studies found no distinction between histological alterations before and after *H. pylori* eradication [5]. However, other studies claimed that eradication helps to improve antral or gastrointestinal somatic lesions [6].

When *H. pylori* was eliminated, the number of neutrophils decreased sharply, whereas the number of monocytes decreased gradually. Endoscopy revealed that medication also reduced hyperplasia and hypertrophic enlargement of the superficial ocular epithelium of metaplastic gastric types (but not intestinal types) [6, 7]. Mixed intestinal metaplasia, however, usually contains more mitotic cells positive for serine-phosphorylated histone H3 proteins than gastric-type cells, regardless of whether *H. pylori* infection is present. Therefore, atrophic gastritis may have undergone irreversible changes when intestinal metaplasia first appeared [5].

According to retrospective studies, 3 years after endoscopic resection of early lesions, *H. pylori* may be successfully eradicated, which may lower the incidence of metachronous GC [8]. However, data from randomized, controlled trials performed for 7.5 years in China indicated that eliminating this microorganism significantly reduced the incidence of gastric adenocarcinoma in patients without atrophy, intestinal metaplasia, or dysplasticemia. There was no appreciable improvement in the overall illness in the eradication group [9]. Another meta-analysis supported the hypothesis that *H. pylori* destruction only affects patients without dysplasia or intraintestinal metaphysis [10].

According to endoscopy results, the digestive tumor area appeared more like gastritis than common malignancies [11]. After the eradication of bacteria, a histopathological analysis of gastric dysplasia (intramucosal adenocarcinoma according to the Japanese criteria) revealed distinct and quick changes in tumor morphology and proliferation characteristics. Additionally, after the administration of antibiotic treatment, gastric tumors seem to be covered in low-grade or normal-grade atypical epithelia [12]. The diagnosis of digestive dysplasia using gastroscopic or histological techniques is made more difficult by these structural changes.

Eradication of H. pylori to prevent the occurrence of metachronous gastric cancer after endoscopic resection of early gastric cancer

Early GC treatments have increasingly benefited from endoscopic resection, which has been extensively used recently. Endoscopic submucosal dissection is one example of these treatments [13]. The risk of metachronous cancer in the model portion of the stomach may be higher than that encountered during medical resection because of the slight invasiveness of endoscopic surgery, which preserves the whole stomach [14]. A study by Choi et al. [15] in 2018 included patients with early GC and other abnormalities. There are no established standards for the period of time until the return to metachronous cancer. Therefore, approximately half of all metachronous cancers are caused by recurrence-related tumors within 1 year. It is possible that the initial test missed these tumors as synchronized lesions. According to studies, *H. pylori* eradication during earlier follow-up appears to lower the risk of metachronous relapse. According to a study with the largest effect size, long-term follow-up revealed that the incidence had increased and there was no apparent way to stop the sophisticated metachronous recurrence of gastric cancer; furthermore, the severity of metachronous recurrence was lower in the eradication group [16]. Another issue is the questionable definition of metachronous recurrence; therefore, further unification of the definition and evaluation criteria is necessary.

Metachronous gastric cancer associated with *H. pylori*: molecular pathogenesis

According to a recent study, *H. pylori*-induced atrophic gastritis and bowel metaplasia, abnormal DNA methylation, epithelial–mesenchymal transition, and GC stem cells are factors that ultimately cause disease. Immune cell recruitment and increased interleukin (IL)-1, tumor necrosis factor, and reactive oxygen species are all induced by serious *H. pylori* infections [17]. Together, these cause DNA methyltransferase-1, which causes activation of the irregular DNA metabolism of the digestive mucosa. Gene-specific eradication of *H. pylori* partly reversed methylation levels in the gastric mucosa, but stem cells continued to methylate some molecules for a very long time. Hence, epigenetic harm of stem cells may be reflected in methylation levels after *H. pylori* eradication [18]. The risk of metachronous GC can be predicted using the microsomal oxidizing system and methylation of miR-124a-3. Patients with metachronous GC have a considerably higher microsomal oxidizing system imprinting level than those with nonmetastatic cancer. Similarly, a higher risk of metachronous GC is linked to high miR-124a-3 imprinting levels [19]. Hence, it is accepted that methylation determined by *H. pylori* is related to metachronous GC.

Impact of *H. pylori* on metachronous precancerous lesions after early gastric cancer endoscopic resection

H. pylori has been linked to intestinal metaplasia and gastric atrophy after endoscopic resection of early GC. Choi et al. and Han et al. found that during a follow-up period of more than 5 years, the *H. pylori* eradication group experienced significantly less gastric corpus atrophy after years of early GC endoscopic treatment [20, 21]. Zhang et al. discovered that *H. pylori* infection is a separate risk factor for gastric mucosal dysplasia after endoscopic resection [22]. A multivariate analysis revealed a link between the incidence of later gastric dysplasia and the eradication of *H. pylori.* Importantly, patients with metachronous gastric dysplasia experienced higher rates of *H. pylori* eradication failure than those with cancer. In other words, in the metachronous group, eradication failure was strongly linked to dysplasia, but never to cancer; hence, *H. pylori* disease may have a role in the improvement of metachronous precancerous injuries after endoscopic resection of early GC. Therefore, *H. pylori* should be eradicated as early as possible after endoscopic resection of early GC to prevent anticipated metachronous precancerous injuries.

Impact of *H. pylori* eradication on metachronous gastric cancer development

The effect of *H. pylori* infection on the emergence of metachronous gastric cancer after endoscopic resection of early GC is still unknown despite the fact that it is a well-known risk factor that significantly contributes to the development of stomach cancer [23]. The mucosa next to *H. pylori*-infected gastric cancer is frequently accompanied by bowel metaplasia and atrophy, and it is more likely to develop metachronous cancer. *H. pylori* contamination is related to an increased risk of gastric dysplasia or cancer after endoscopic resection of early GC, and *H. pylori* disease is related to the risk of metachronous GC after endoscopic submucosal dissection of early GC [17].

It is debatable whether eliminating *H. pylori* may prevent metachronous cancer development after endoscopic excision of early GC. However, according to multiple meta-analyses, eliminating *H. pylori* can greatly lower the occurrence of metachronous stomach cancer and, hence, avoid it in patients who have undergone endoscopic resection [24]. The Maastricht Consensus Report and Japanese Society of Gastroenterology recommendations still recommend the elimination of *H. pylori* after endoscopic resection of early GC, regardless of the possibility that metachronous GC might arise after successful cure of *H. pylori* infection [25]. More prospective trials and long-term follow-up are necessary to determine the role of *H. pylori* removal in the prevention of metachronous GC after endoscopic resection of early GC.

Long-term effects of gastric cancer-related epigenetic changes induced by H. pylori eradication

Long-term research performed in Japan demonstrated that digestive atrophic mucosa is associated with the risk of GC after *H. pylori* is eradicated because these noncancerous diseases develop decades after *H. pylori* therapy [26]. Biological and epigenetic changes accumulate to form GC. Numerous studies have identified a number of molecular changes linked to digestive precancerous lesions and cancer as well as hereditary instability and the promoter methylation of numerous tumor-related genes [27]. These studies have also reported a number of biomarkers associated with cancer risk. Currently, it is thought that dysregulation of noncoding RNAs, such as miR-124a-3 methylation, also contributes significantly to GC pathogenesis [28,29]. Although some studies have evaluated changes in molecular alterations after *H. pylori* eradication, the follow-up period seems to be brief, typically lasting less than 3 years. According to a randomized, controlled trial in Japan, endoscopic resection of early GC to eradicate *H. pylori* could delay the onset of metachronous GC for up to 3 years; furthermore, according to further long-term follow-up studies conducted in Japan, the elimination of *H. pylori* did not diminish the incidence of metachronous GC more than 5 years after endoscopic resection. In summary, to fully understand the chemopreventive effects of eliminating *H. pylori* on molecular changes, long-term research for least 3 years may be necessary.

An essential epigenetic mechanism of carcinogenesis, *H. pylori* infection, causes aberrant DNA methylation of certain genes and promotes the CpG island methylation phenotype [30]. Methylation is believed to be associated with epigenetic changes in noncancerous cells. With the removal of *H. pylori*, CpG island methylation phenotype frequencies in patients without island methylation significantly decreased, indicating widespread CpG island methylation, including methylation of several genes and loci, including CDH1 (which is a transcriptional regulator of E-cadherin), CDKN2A (which is a cellular cell cycle-dependent kinase inhibitor gene), MSX2 interacting nuclear target protein 1, and MSX2 interacting nuclear target protein 31. According to previous research, CDH1 methylation is commonly found in precancerous lesions and is strongly associated with *H. pylori* infection [31].

A recent meta-analysis revealed a strong correlation between MGMT hypermethylation and an increased risk of GC, particularly in Asians [30]. To establish the connection between changes in methylation of these genes after *H. pylori* eradication and GC development, long-term follow-up studies with larger sample sizes are required.

Numerous tumor suppressor miRNAs exhibit DNA hypermethylation in the promoter CpG island of GC, leading to silencing [32, 33]. *H. pylori* infection has been reported to cause DNA methylations of miRNA genes [32]. Recent studies have shown a link between the risk of metachronous GC and miR-124a-3 methylation in the gastric mucosa. The idea of a "cancerous epigenetic field," particularly in the GC group, may be strongly supported by the discovery that ethylation is common in the stomach. A recent study by Huang et al. [33, 34], consistent with the study by Michigami et al. showed noticeably different methylation patterns between the antrum and corpus or cardia. The GC group had higher reactivity throughout the entire stomach [34], whereas the corner of the stomach had the highest incidence of Das-1 monoclonal antibody. The *H. pylori*-positive and *H. pylori*-negative groups had a significantly higher incidence of Das-1 monoclonal antibody reactivity than the control group.

Chemoprevention of gastric cancer after eradication of H. pylori

Oxygen free radical scavengers

It is believed that the use of natural products lowers the risk of GC [35]. Therefore, as mediators of DNA deterioration and carcinogen production, inflammation and oxidative stress are crucial for the development of GC. Because the severity of inflammation is the primary factor influencing the development of GC, it may be more logical to eradicate bacteria and reduce inflammation. To prevent gastric inflammation and carcinogenesis in treated animals, the Mongolian gerbil model was used to examine the effects of 4-vinyl-2,6-dimethoxyphenol, which is one of the most potent antioxidant compounds extracted from crude rapeseed oil, on *H. pylori* infection and carcinogens. Furthermore, 0.1% canolol was added to food to inhibit cyclooxygenase 2 (COX-2), nitric oxide synthase, and 8-hydroxy-2'-deoxyguanosine. Despite survival, the incidence of gastric adenocarcinoma was significantly lower, and *H. pylori* levels remained unchanged [36]. In K19-C2mE transgenic mice, canolol at 37°C also prevented the development of spontaneous gastric tumors by lowering COX-2, IL-1β, and IL-12β levels, possibly by activating the tumor suppressor miR-7 microRNA [37]. These findings suggest that the most crucial element in the development of cancer may not be the presence of *H. pylori*, but rather the degree of inflammation.

COX-2 inhibitors

The inflammatory microenvironment and cancer are two processes significantly influenced by COX-2 and its downstream products. The overexpression of COX-2 has been linked to colorectal and stomach cancers in mouse models. Celecoxib and other COX-2 selective inhibitors, such as etodolac, may have chemopreventive effects that not only reduce inflammation but also result in the regression of tumors [38]. With *H. pylori* removal, COX-2 inhibitors stimulate the regression of precancerous lesions and stop the development of stomach cancer in individuals with severe metaplastic gastritis. During a nonrandomized experiment, Yanaoka et al. [39] administered etodolac to patients who had positive serum pepsinogen tests but negative *H. pylori* antibodies and discovered that it was helpful for preventing the growth of metachronous cancer. Furthermore, another study utilized the COX-2 inhibitor celecoxib during an intercession trial conducted in conjunction with *H. pylori* annihilation, which caused relapse of gastric injuries and uncovered the significance of the COX-2–prostaglandin E2 pathway [40].

Conclusion

In conclusion, GC is primarily caused by *H. pylori* infection. According to estimates, *H. pylori* infection is responsible for 90% of all GC cases. Therefore, the primary strategy for preventing the development of GC is the eradication of *H. pylori*. According to previous studies, the incidence and mortality rates of GC can be significantly decreased by *H. pylori* eradication. A large team of prevention and treatment personnel as well as sizable funding are needed because of the large number of infected individuals. The responsibility rests with medical professionals because the *H. pylori* vaccine is still being developed. First-line treatment for early GC is endoscopic submucosal dissection in Japan, Korea, and China because of the possibility of removing all of the GC [41]. However, it is anticipated that patients without GC but with gastritis are at higher risk for metachronous carcinoma after endoscopic resection. The risks of residual gastroenteritis and metachronous carcinoma attributable to severe atrophic gastritis are other drawbacks of endoscopic resection and surgical resection. Small, differentiated intramucosal carcinomas smaller than 20 mm typically present with metachronous GC. Within 3 to 5 years of endoscopic resection, metachronous cancer is found in 2.7% to 15.6% of patients [42]. Therefore, it is crucial to lower the incidence of metachronous cancer after endoscopic resection.

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