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Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Ai-Wen Wu, MD, PhD, Professor, Department of GI Surgery, Key laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University Cancer Hospital and Institute, Beijing 100142, China

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Ya-Juan Ma, Director
World Journal of Gastrointestinal Oncology
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Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
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PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
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MINIREVIEWS

Risk of gastric cancer development after eradication of *Helicobacter pylori*

Ka-Shing Cheung, Wai K Leung

Ka-Shing Cheung, Wai K Leung, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China

ORCID number: Ka-Shing Cheung (0000-0002-4838-378X); Wai K Leung (0000-0002-5993-1059).

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Correspondence to: Wai K Leung, MB, ChB, MD, MRCP, Doctor, Professor, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China. waikleung@hku.hk
Telephone: +86-852-22553348
Fax: +86-852-28162863

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Abstract

Helicobacter pylori (*H. pylori*) infection is the most important risk factor for gastric cancer (GC) development through the Correa's gastric carcinogenesis cascade. However, *H. pylori* eradication alone does not eliminate GC, as pre-neoplastic lesions (atrophic gastritis, intestinal metaplasia and dysplasia) may have already developed in some patients. It is therefore necessary to identify patients at high-risk for gastric cancer after *H. pylori* eradication to streamline the management plan. If the patients have not undergone endoscopy with histologic assessment, the identification of certain clinical risk factors and non-invasive testing (serum pepsinogen) can predict the risk of atrophic gastritis. For those with suspected atrophic gastritis, further risk stratification by endoscopy with histologic assessment according to validated histologic staging systems would be advisable. Patients with higher stages may require long-term endoscopic surveillance. Apart from secondary prevention to reduce deaths by diagnosing GC at an early stage, identifying medications that could potentially modify the GC risk would be desirable. The potential roles of a number of medications have been suggested by various studies, including proton pump inhibitors (PPIs), aspirin, statins and metformin. However, there are currently no randomized clinical trials to address the impact of these medications on GC risk after *H. pylori* eradication. In addition, most of these studies failed to adjust for the effect of concurrent medications on GC risk. Recently, large population-based retrospective cohort studies have shown that PPIs were associated with an increased GC risk after *H. pylori* eradication, while aspirin was associated with a lower risk. The roles of other agents in reducing GC risk after *H. pylori* eradication remain to be determined.

Key words: Gastric adenocarcinoma; Stomach cancer; *Helicobacter pylori*; Chemoprevention; Intestinal metaplasia

Core tip: Although *helicobacter pylori* (*H. pylori*)

infection is the most important risk factor for gastric cancer (GC) development, eradication of this bacteria does not guarantee the elimination of GC risk, as pre-neoplastic lesions may have already developed. It is therefore necessary to identify patients at high-risk for GC after *H. pylori* eradication by either endoscopy with histologic assessment or non-invasive testing. Long-term endoscopic surveillance is advisable for high-risk patients. Future studies are necessary to investigate medications that may modify the GC risk after *H. pylori* eradication.

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INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer worldwide, with an estimation of 952000 new cases (6.8% of all incident cancer cases) in 2012[1]. The disease burden is particularly high in East Asian countries where around half of the new cases are diagnosed. It is the third leading cause of cancer related mortality in the world, with 723000 deaths (8.8% of all cancer deaths) in a year. Around two-thirds of patients are diagnosed with GC at an advanced stage when curative surgery is not possible[2,3]. Despite the advances in surgery and chemotherapy, the prognosis remains dismal in patients with advanced disease, with a median survival of less than one year.

The global prevalence of *Helicobacter pylori* (*H. pylori*) infection in adults ranges from 19% to 88%[4]. *H. pylori* infection is one of the major risk factors for GC development (a relative risk of 2.8 as shown in a recent meta-analysis)[5]. It is estimated that *H. pylori* infection attributes to 89% of non-cardia GC cases, which in turn accounts for 78% of all GC cases[6]. *H. pylori* is classified by the International Agency for Research on Cancer of the World Health Organization as class I human carcinogen[7]. It is postulated that *H. pylori* infection triggers and promotes the Correa's cancer cascade[8]– a multistep process involving sequential changes of the gastric mucosa from chronic gastritis to atrophic gastritis, intestinal metaplasia, dysplasia and finally adenocarcinoma. Atrophic gastritis, intestinal metaplasia and dysplasia are considered to be pre-neoplastic lesions. In a population-based cohort study, the risk of GC was increased in patients with atrophic gastritis, intestinal metaplasia and dysplasia as compared to those with normal gastric mucosa by a hazard ratio (HR) of 4.5, 6.2 and 10.9, respectively[9].

H. PYLORI ASSOCIATED GC

There are multiple pathways by which *H. pylori* leads to GC development. *H. pylori* incites acute-on-chronic inflammation, leading to a high turnover rate of gastric epithelium as well as a microenvironment in which high levels of reactive oxygen and nitrogen radicals promote persistent DNA damage[10-13]. *H. pylori* can also induce epigenetic changes including CpG island methylation of tumor suppressor genes such as E-cadherin[14,15]. The aberrant expression of activation-induced cytidine deaminase *via* the effect of nuclear factor (NF)-κB can alter nucleotides in the tumor-related genes[16,17]. The induction of double-stranded DNA breaks and alteration of microRNAs expression further contribute to the genetic instability[11,18]. The interplay between *H. pylori,* gastric microbiome and the exogenous factors in producing carcinogens further adds complexity to the *H. pylori*-induced carcinogenesis[18]. *H. pylori* eradication can reduce or even eliminate gastric mucosal inflammation and reverse the *H. pylori*-associated molecular events[15,18].

GC AFTER *H. PYLORI* ERADICATION

Although *H. pylori* is a major risk factor of GC, eradication of *H. pylori* does not completely eliminate the risk of subsequent GC development. It has been shown that *H. pylori* eradication could only reduce GC by 33%-47%[19,20]. The fact that a significant proportion of *H. pylori*-eradicated subjects progress to develop GC is likely related to the baseline gastric histology at the time of eradication. The development of pre-neoplastic lesions including atrophic gastritis, intestinal metaplasia and dysplasia undermines the effect of *H. pylori* eradication in reducing GC[21,22]. In a prospective, randomized study involving 1630 *H. pylori*-infected subjects conducted by Wong *et al*[21], the beneficial effect of *H. pylori* eradication was limited to patients without baseline pre-neoplastic lesions (atrophic gastritis, intestinal metaplasia and dysplasia). No GC was diagnosed among patients who received *H. pylori* eradication therapy without pre-neoplastic lesions during a follow-up of 7.5 years. A meta-analysis of 10 studies involving 7955 patients by Chen *et al*[22] also showed similar findings.

H. pylori eradication is found to reverse chronic gastritis in the majority of patients and atrophic gastritis in some patients[23-25], but not for intestinal metaplasia[24,26]. The presence of intestinal metaplasia is therefore considered to be a "point of no return" in the GC cascade. However, *H. pylori* eradication has been shown to slow the progression of intestinal metaplasia to GC[25,27]. A study of 2258 patients with a much longer follow-up duration (up to 15 years) showed that *H. pylori* eradication reduced GC risk even in those with intestinal metaplasia and dysplasia[28]. In concordance with this study, a randomized controlled trial of 544 patients concluded that *H. pylori* eradication after endoscopic resection of early GC could reduce the risk of metachronous GC by 65%[29]. Since most of these patients with early GC would have concurrent pre-neoplastic lesions in the stomach, the findings would

support the potential benefits of *H. pylori* eradication to prevent GC development even in the presence of advanced gastric histology.

A recent nationwide population-based study from Sweden showed that treatment for *H. pylori* could reduce GC and non-cardia GC development when compared to background population[30]. Overall, about 0.2% of patients developed GC after *H. pylori* treatment. However, the risk reduction was only apparent 5 years after *H. pylori* eradication treatment (standardized incidence ratio of 0.31), suggesting a long lag time of benefits by chemoprevention.

SURVEILLANCE FOR HIGH-RISK PATIENTS AFTER *H. PYLORI* ERADICATION

Eradication of *H. pylori* before the development of atrophic gastritis can nearly eliminate GC risk[31]. As discussed, among patients who have already developed atrophic gastritis, eradication of *H. pylori* can only halt and partially reverse the progression of gastric mucosal damage, and therefore this group of patients is still at increased risk for GC development. According to the Kyoto Global Consensus statement[32], patients with *H. pylori* infection diagnosed non-invasively and at risk for atrophic gastritis should undergo endoscopy for histological assessment. These risk factors include age range in which atrophic gastritis are prevalent in that particular population, a prior history of gastric ulcer, a pretreatment serum pepsinogen Ⅰ level of less than 70 ng/mL and a pepsinogen Ⅰ : Ⅱ ratio of less than 3. The degree and extent of atrophic gastritis and intestinal metaplasia are important in predicting subsequent GC risk. Two validated histologic staging systems, Operative Link for Gastritis Assessment (OLGA)[33] and Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM)[34], have been proposed for further risk stratification. Those with OLGA or OLGIM stages Ⅲ-Ⅳ are considered to be at high risk of GC development, and may be considered for a long-term endoscopic surveillance program[31]. Surveillance programs are considered to be cost effective only in this group of high-risk patients[32,35,36]. The aims of secondary prevention programs are to remove intraepithelial lesions and early GC before the lesions become invasive, thereby reducing GC-related deaths[31,32]. Currently, there are insufficient data to guide the optimal management strategies for patients with lower OLGA and OLGIM stages. Even the optimal surveillance intervals for high risk patients are based on expert opinions rather than data from clinical trials[37].

ROLES OF MEDICATIONS IN GC DEVELOPMENT AFTER *H. PYLORI* ERADICATION

There are still sparse data on the modifiable risk factors for GC after *H. pylori* eradication. Increasing evidence has emerged showing that certain medications may increase GC risk, while some are shown to reduce cancer risk. However, the majority of these studies included both *H. pylori*-infected and *H. pylori*-negative subjects. In the following sections, medications that could potentially modify GC risk after *H. pylori* eradication, including proton pump inhibitors (PPIs), aspirin, cyclooxygenase-2 (COX-2) inhibitors, statins, metformin as well as lifestyle factors will be discussed. Their effects are summarized in Table 1.

Proton pump inhibitors

Since its introduction in the 1980s, PPIs have become one of the most commonly prescribed medications worldwide[38]. PPIs lead to profound acid suppression which could worsen atrophic gastritis[39], particularly in *H. pylori*-infected subjects[40]. In addition, the increase in gastrin (a potent growth factor that has trophic effect on gastric mucosa) in response to the hypochlorhydria would stimulate enterochromaffin-like cell hyperplasia[40]. A meta-analysis of four studies (one cohort and three case-control studies) showed that the risk of GC was increased by 43% among PPI users[41]. However, the *H. pylori* status was unknown in these studies, and multiple biases including protopathic and indication biases were present.

Recently, we conducted a territory-wide retrospective cohort study recruiting 63397 *H. pylori*-eradicated subjects[42]. PPIs use (defined as at least weekly use) was shown to be associated with an increased GC risk (HR = 2.44) even after *H. pylori* eradication, while histamine-2 receptor antagonists (H2RA) were not a significant risk factor. Compared with non-PPIs use, the risk increased with increasing frequency (HR 2.43 for weekly to less than daily use, and HR 4.55 for daily use) and duration of PPIs use (HR = 5.04, 6.65 and 8.3 for ⩾ 1 year, ⩾ 2 years and ⩾ 3 years, respectively). The adjusted absolute risk difference for PPIs *vs* non-PPIs use was 4.29 excess GC cases per 10000 person-years. H2RA was chosen as a negative control exposure in this study to address the issue of indication bias. Prescriptions of PPIs and H2RA within six months prior to GC diagnosis were excluded to reduce protopathic bias. One intriguing observation from this study was that the cohort of PPIs users who had not received *H. pylori* eradication therapy had the lowest incidence rate of GC (0.8 per 10000 person-years) when compared to that of the two *H. pylori*-eradicated cohorts with and without PPIs use (8.1 and 2.9 per 10000 person-years, respectively). It thus appears that prior *H. pylori* infection is still a more important risk factor than PPIs use in the determination of GC risk, and PPIs increase GC risk only in those with baseline pre-neoplastic lesions induced by prior *H. pylori* infection. The study, however, did not investigate whether the increased GC risk existed for all kinds of PPIs.

Aspirin

Recent meta-analyses investigating the potential role of aspirin concluded that aspirin was associated with

Table 1 Pharmacological modalities to reduce risk of gastric preneoplastic lesions and/or cancer

References	Drugs	Study design	Number of subjects	Results
You *et al*[92], 2006	Vitamin and garlic supplement	Randomized controlled trial	3365	No protective effect
Leung *et al*[56], 2006	Rofecoxib	Randomized controlled trial	213	Regression of IM: (a) antrum (24.5% *vs* 26.9% for placebo) (b) corpus (4.3% *vs* 2.2% for placebo)
Wong *et al*[57], 2012	Celecoxib	Randomized controlled trial	1024	OR of IM regression: (a) celecoxib alone (OR = 1.72; 95%CI: 1.07-2.76) (b) H. pylori eradication followed by celecoxib (OR = 1.48; 95%CI: 0.91-2.40)
Cheung *et al*[53], 2018	Aspirin	Population-based retrospective cohort study	63605	PS-adjusted HR of GC: 0.30 (95%CI: 0.15-0.61)
Cheung *et al*[42], 2018	Proton pump inhibitors	Population-based retrospective cohort study	63397	PS-adjusted HR of GC: 2.44 (95%CI: 1.42-4.20)

IM: Intestinal metaplasia; OR: Odds ratio; PS: Propensity score; HR: Hazard ratio; GC: Gastric cancer.

a reduced GC risk in observational studies, while post-hoc analysis of randomized trials showed statistically non-significant trend favoring aspirin use[43,44]. The chemopreventive effect of aspirin is mediated *via* both cyclooxygenase (COX)-2 and non-COX related pathways, including phosphatidylinositol 3-kinase (PI3K)[45,46], NF-κB[47], Wnt-β-catenin, extracellular signal-regulated kinase (ERK) and activated protein1 (AP-1)[48].

However, most published data included both *H. pylori*-infected and *H. pylori*-negative subjects. A few studies showed that the chemopreventive effect of aspirin was higher in *H. pylori*-infected subjects on stratified analysis[49-51]. As shown in a case-control study, the chemopreventive effect of aspirin use was higher in *H. pylori*-infected subjects [odds ratio (OR) = 0.39] than in the whole cohort (OR = 0.60), and no statistically significant difference was noted for *H. pylori*-negative subjects[50]. Another population-based study from Sweden showed that the ORs were 0.70 for the whole cohort and 0.60 for *H. pylori*-infected subjects, again without statistically significant difference for *H. pylori*-negative subjects[51]. Similarly, a Taiwanese nationwide retrospective cohort study found that the HR of GC with regular use of non-steroidal anti-inflammatory drugs (NSAIDs) was lower for *H. pylori*-infected (HR = 0.52) than non-infected subjects (HR = 0.80)[52].

A recent territory-wide retrospective cohort study recruiting 63605 *H. pylori*-eradicated subjects showed that aspirin use (defined as at least weekly use) was associated with a reduced GC risk (HR = 0.30)[53]. The protective effect increased with increasing frequency, duration and dose of aspirin (all *P*-trend < 0.001), being most prominent in those who used aspirin daily (HR = 0.21), for at least 5 years (HR = 0.07) and at a dose of at least 100 mg (HR = 0.15). The protective effect of aspirin appeared to be larger in *H. pylori*-eradicated subjects (HR = 0.30) than that reported by a meta-analysis including both *H. pylori*-infected and *H. pylori*-negative subjects (pooled OR = 0.78)[43]. This should be interpreted with caution, however, as it is not a head-to-head comparison with different patient characteristics.

However, one of the major side effects of aspirin is gastrointestinal bleeding, and the risk-benefit profile of aspirin use on GC prevention in *H. pylori*-infected subject remains to be determined. The adjusted absolute risk difference was only 2.52 fewer GCs per 10000 person-years for aspirin users after *H. pylori* eradication[53]. Future studies to address the risk-benefit profile are warranted. Nonetheless, the evidence from this territory-wide cohort study may provide further support for aspirin use in the consideration of the risk-benefit profile of aspirin use in preventing cardiovascular events and various cancers. The United States Preventive Services Task Force favors the use of low-dose aspirin for the primary prevention of cardiovascular disease and colorectal cancer in adults aged 50 to 59 years who have a more than 10% 10-year risk of cardiovascular disease and are not at increased risk of bleeding[54].

COX-2 inhibitors

COX-2 is an enzyme involved in the conversion of arachidonic acid to prostaglandins, and its overexpression is found in gastric intestinal metaplasia and cancer[55]. Two randomized trials have been performed to evaluate the potential benefit of COX-2 inhibitors[56,57]. In the study of 213 *H. pylori*-eradicated subjects with intestinal metaplasia, the use of rofecoxib did not significantly regressed intestinal metaplasia and its severity over 2 years[56]. The study by Wong et al showed that celecoxib use for 2 years could regress advanced gastric lesions in *H. pylori*-infected subjects, but a synergistic effect was not observed in those who had *H. pylori* eradicated[57].

Statins

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is one of the key enzymes for cholesterol synthesis[58], and are widely used for the primary and secondary prevention of cardiovascular diseases. Besides, it has been proposed to have chemo-preventive effects on solid organ tumors in *in-vitro* studies, by halting cell-cycle progression[59], inducing

apoptosis[60], inhibiting angiogenesis[61], and inhibiting the growth of tumor cells[62].

To date no data from randomized clinical trials are available concerning the role of statins in GC prevention. A meta-analysis[63] of 11 studies (eight observational, three post-hoc analyses of 26 clinical trials) reported a significant reduction in GC risk with statin use (adjusted OR = 0.68), in a dose-dependent manner. However, conflicting results exist among observational studies, with some showing statins to be protective against GC[64-67], while no such benefit was observed in other studies[68-74]. This is likely due to the heterogeneity of different studies, and the recruitment of both *H. pylori*-infected and *H. pylori*-negative subjects. The confounding effect of *H. pylori* would significantly affect the causal relationship and the magnitude of any beneficial effect. Therefore, studies dedicated to investigate the chemopreventive effect of statin on GC after *H. pylori* eradication are warranted.

Metformin

An increased GC risk by around 19% among patients with diabetes mellitus (DM) was reported by a meta-analysis of 17 studies (11 cohort studies, six case-control studies)[75]. But among diabetic patients who take metformin, the GC risk appears to be lower[76]. The anti-cancer activity by metformin is proposed to be mediated by two pathways. First, as metformin is an insulin sensitizer, it reduces the production of insulin and insulin-growth factors (IGFs). Proliferation of cancer cells expressing IGF receptors is stimulated by the IGFs signaling pathway[77]. Second, the activation of AMP-activated protein kinase (AMPK) and the subsequent inhibition of the mammalian target of rapamycin pathway is shown to inhibit the growth of cancer cells[78].

A recent meta-analysis of seven cohort studies concluded that metformin use was associated with a reduced GC risk (HR = 0.76)[76]. However, significant heterogeneity was noted among these studies. The chemopreventive role of metformin remains controversial in clinical studies, as data from randomized clinical trials are not available. While a protective effect with varying effect estimate was shown for some studies[79-83], others failed to demonstrate such association[84,85]. The failure to adjust for *H. pylori* infection and the severity of DM further complicates the debate over this issue.

A population-based cohort study of 2603 Japanese subjects showed the GC risk was larger with higher hemoglobin A1c (HbA1c) levels[86]. The age- and sex-adjusted incidence of GC among individuals with HbA1c levels of 5.0%-5.9%, 6.0%-6.9% and ⩾ 7.0% were 2.5, 5.1, and 5.5 per 1000 person-years. *H. pylori* infection and a higher HbA1c level (⩾ 6.0%) had a synergistic effect on increasing GC risk. The protective effect of metformin on GC may therefore be due to a better DM control instead of the anti-cancer effects found in *in-vitro* studies. This study, however, did not adjust for the effect of various medications and comorbidities, and therefore the independent role of HbA1c level remains to be determined.

Future studies to include a homogenous group of patients (*i.e.*, only *H. pylori*-eradicated subjects) and factor in the effect of DM control (as reflected by HbA1c level) as well as medications that may modify cancer risk are crucial to investigate (1) the chemopreventive role of metformin in GC in diabetic patients; and (2) whether HbA1c is an independent risk factor for GC. As HbA1c is a time-varying covariate, not only the baseline HbA1c level but also the dynamics throughout the follow-up should be taken into consideration in order to derive a more precise effect estimate.

Lifestyle factors

Lifestyle factors that could potentially affect the risk of preneoplastic lesions and GC include smoking, alcohol use, high salt intake, vitamins and antioxidants. Concentrated salt intake is proposed to cause excessive cell replication (hence increased rate of endogenous mutations), to incur mucosal damage with associated inflammatory changes and to induce atrophic changes in gastric mucosa[87]. Ascorbic acid, on the other hand, is linked with a protective effect against intestinal metaplasia and GC by reducing the gastric pH[88]. Atrophic gastritis favors the proliferation of anerobic bacteria which reduce nitrate (abundant in various kinds of food) to nitrite, in turn reacting with other nitrogen-containing components to generate N-nitroso carcinogens.

However, data on the roles of these factors in *H. pylori*-eradicated subjects are lacking. A randomized control trial on *H. pylori* eradication showed that alcohol consumption (OR = 1.67) was independently associated with intestinal metaplasia progression[89]. Another study of more than 3000 Chinese subjects with baseline chronic atrophic gastritis showed that the risk of transition to dysplasia nearly doubled among smokers while the risk of intestinal metaplasia was mildly increased[90]. In another study involving 3433 patients, the risk of progression to dysplasia or GC increased with increasing years of cigarette smoking, but decreased among those with higher levels of ascorbic acid (OR = 0.2, highest *vs* lowest tertile)[91].

The roles of vitamin and antioxidant supplements also remain controversial as shown by a three-arm trial which randomized 3365 *H. pylori*-infected subjects to eradication therapy, vitamin supplement (vitamin C, vitamin E and selenium) and garlic supplement (aged garlic extract and steam-distilled garlic oil)[92]. While *H. pylori* treatment reduced the risk of preneoplastic lesions and GC, similar beneficial effect was not observed for vitamin or garlic supplements.

CONCLUSION

H. pylori infection is the most important risk factor for GC development. However, *H. pylori* eradication does not entirely eliminate the GC risk, as pre-neoplastic

lesions (atrophic gastritis, intestinal metaplasia and dysplasia) may have already developed. It is therefore necessary to identify patients at high risk for GC after *H. pylori* eradication to streamline the management plan. The detection of atrophic gastritis by non-invasive testing (serum pepsinogen) or endoscopy with histologic assessment, followed by further risk stratification with validated histologic staging systems (*e.g.*, OLGA and OLGIM) would be advisable. Patients with higher stages may require regular endoscopic surveillance. Apart from secondary prevention to reduce deaths by diagnosing GC at an early stage, identifying medications that could potentially modify the GC risk would be desirable. The potential roles of a number of medications have been suggested by various studies, including PPIs, aspirin, statins and metformin. However, several drawbacks need to be acknowledged. First, there are currently no randomized clinical trials to address the impact of these medications on GC risk. Second, the majority of these studies recruited both *H. pylori*-infected and *H. pylori*-negative subjects, but not specifically *H. pylori*-eradicated ones. In addition, previous studies failed to adjust for the effect of concurrent medications on GC risk. The failure to take into account the effect of *H. pylori* infection and concurrent medications will undoubtedly bias the causal relationship and the effect estimate. Recently, large population-based retrospective cohort studies have shown that PPIs were associated with an increased GC risk after *H. pylori* eradication, while aspirin was protective. The roles of statin and metformin in reducing GC risk after *H. pylori* eradication remain to be determined.

Owing to the relatively low incidence of GC and the long lag time of cancer development, investigating the potential modifiable factors (including medications) for GC development by randomized clinical trials would require a large sample size and long follow-up duration which are technically difficult and resource-intensive. Future research should focus on high-risk population including those with underlying pre-neoplastic lesions, family history of GC or those who have undergone endoscopic removal of early gastric tumors. Another research direction would be the use of population-based retrospective cohort study design for pharmaco-epidemiological studies on GC. As such, studies can be carried out in a short period of time with large sample size, despite the relatively rare incidence of GC. We have previously examined the effects of PPIs and aspirin among *H. pylori*-eradicated subjects in population-based retrospective cohort studies. There are still other potential chemopreventive agents that remain to be explored, for example, statins and metformin. The concept of "drug repurposing" has recently been advocated in the field of oncology: Currently approved drugs with a non-oncology primary purpose may be used for chemoprevention or as an adjunctive treatment. The use of population-based retrospective cohort studies can help in identifying potential drug candidates and directing the path to future randomized clinical trials.

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