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Chemoprevention Against Gastric Cancer

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BACKGROUND

Gastric cancer is the fifth most common cancer and third leading cause of cancer-related mortality globally, accounting for approximately 1 million new cases annually and more than 780,000 cancer-related deaths.[1] Prevention and early detection are two foundational pillars for addressing the substantial burden of gastric cancer. Early detection provides the opportunity for potentially curative resection if gastric cancer is diagnosed before submucosal invasion. However, except in the few countries where endoscopic screening for gastric cancer occurs, gastric cancer is most often diagnosed in the advanced stages, which is when symptoms present and prompt a diagnostic evaluation. Unfortunately, there are no curative options for advanced stage disease and the 5-year survival rates are dismal at best. The vast majority of countries, including the United States, do not screen for gastric cancer. Focused efforts on gastric prevention, therefore, are key and represent the mainstay in these countries. Attention to primary, secondary, and tertiary gastric cancer prevention, even in those countries where gastric cancer screening does occur, decreases the downstream health and economic burden associated with a gastric cancer diagnosis.

Cancer risk determinants can be divided into modifiable (eg, diet, smoking) and nonmodifiable (eg, genetics, age) factors. Accordingly, interventions aimed at cancer risk attenuation and prevention are focused on altering modifiable factors; for example, via smoking cessation and nutritional education programs. Chemoprevention is a critical adjunct, because these interventions alone are rarely sufficient. Chemoprevention in the form of *Helicobacter pylori* eradication already forms the foundation for gastric cancer prevention. However, the benefit is significantly attenuated once more advanced gastric mucosal changes have occurred, because the risk of gastric cancer persists despite *H pylori*

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eradication. As described elsewhere in this article, *H pylori* eradication therapy decreases but does not eliminate the risk of metachronous cancer (tertiary prevention), thus suggesting that there is a field effect that persists even in the absence of ongoing *H pylori* infection. Further complicating the picture is that there is an increase in observed non–*H pylori* associated noncardia gastric adenocarcinoma in some populations, particularly as the prevalence of *H pylori* decreases.[2] For these reasons, chemopreventive agents aside from *H pylori* eradication alone should likewise be considered tenets to any successful gastric cancer control program.

In this article, we will discuss chemopreventive agents for intestinal-type noncardia gastric cancer, with a predominant focus on *H pylori* eradication therapy and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, because these agents have the strongest and largest body of supporting data. Other putative chemopreventive agents are discussed within the context of both clinical and experimental data.

Mechanisms

Having an in-depth understanding of the pathogenesis of intestinal-type noncardia gastric adenocarcinoma (NCGA), along with modifying factors, is foundational to chemoprevention research and the discovery of effective chemopreventive agents. NCGA develops as a stepwise progression from chronic nonatrophic gastritis to atrophic gastritis, intestinal metaplasia, and dysplasia, before the final malignant transformation in a very small proportion of individuals.[3,4] The most common trigger for this so-called Correa cascade is chronic infection with *H pylori*. Three nested case-control studies, all published in 1991, demonstrated that people with *H pylori* infection had a significant 3-fold to 6-fold higher likelihood of developing gastric cancer compared with individuals without *H pylori* infection.[5–7] Accordingly, the World Health Organization and International Agency for Research on Cancer classified *H pylori* as a definite biological carcinogen. A meta-analysis published by the Helicobacter and Cancer Collaborative Group in 2001 with 10 additional years of data confirmed these findings.[8] Even though only a small percentage of individuals infected with *H pylori* (<1%–3%) will have malignant complications, this number still represents a massive burden of preventable disease because *H pylori* is estimated to infect more than one-half the global population; indeed, approximately 90% of NCGA are attributable to *H pylori* infection.[9–11] Other environmental triggers for the inflammation–preneoplasia–neoplasia sequence, including chronic bile reflux, high dietary consumption of salt and nitrites, the non–*H pylori* microbiome and metabolic byproducts, and autoimmunity, can act independently or potentiate the pathologic effects of *H pylori*.[12]

The complex interactions between these triggers, along with underlying host genetic factors and microbial factors, including *H pylori* strain–specific factors, together lead to a field effect of gastric mucosal changes; however, the exact molecular and genetic underpinnings remain unclear. Depending on ongoing insults, progression may or may not occur. DNA damage, as the downstream consequence of ongoing inflammation and subsequent oxidative stress, is a fundamental process in gastric carcinogenesis, even in the absence of *H pylori*. One study in a Mongolian gerbil experimental model demonstrated that administering a diet containing a potent antioxidant derived from canola oil (4-vinyl-2,6-dimethoxyphenol) resulted in a substantially lower incidence of gastric adenocarcinoma,

even though the *H pylori* bacterial density was not changed.[13] Similar findings were replicated in transgenic mice, where administration of 4-vinyl-2,6-dimethoxyphenol was associated with significantly lower levels of cyclo-oxygenase (COX)-2, IL-1B, and IL-12B expression and significantly lower likelihood of spontaneous gastric tumor development.[14] Collectively, these data confirm that inflammation severity, not just *H pylori* infection alone, is likely the more important factor in NCGA pathogenesis and underscores the importance of chemopreventive strategies apart from simply *H pylori* eradication alone.

H pylori Eradication Treatment as Chemoprevention Against Gastric Cancer

H pylori typically persists for the lifetime of the host unless eradicated with antibiotics and high-dose acid suppression for a set duration. Before the formal discovery of *H pylori* by J. Robin Warren and Barry Marshall in the late 1970s,[15] the environmental trigger for the Correa cascade was unknown and was thought most likely to be dietary. Several subsequent studies unequivocally confirmed that chronic *H pylori* infection led to chronic gastritis with or without continued progression along the carcinogenic cascade.[6–8,16]

Since that time, several observational and interventional studies evaluating the effect of *H pylori* eradication versus no eradication on gastric cancer incidence have been published, albeit with mixed results, because some studies have yielded null findings. The mixed results likely reflect differences in study population, design, length of follow-up, presence of preneoplastic lesions at the time of *H pylori* eradication, the exposure measure (eg, *H pylori* eradication treatment but without subsequent confirmation testing as the exposure group vs *H pylori* eradication treatment and confirmed successful eradication as the exposure group), outcome measures (eg, some studies analyzed changes in atrophic gastritis or gastric intestinal metaplasia as surrogate markers, and not gastric cancer incidence per se), and the reference population (eg, general population as the reference group vs individuals with *H pylori* infection but who received placebo/no treatment, or unsuccessful treatment as the reference group), among others. Prospective large population-based studies are no longer likely to be performed, especially in countries with low to intermediate gastric cancer incidence, owing to cost and logistical barriers, not to mention ethical considerations.[17] The long sojourn time between *H pylori* infection and gastric cancer occurrence and the overall rarity of gastric cancer on a population level are leading barriers for such studies. For chemoprevention trials, follow-up should ideally extend past 10 years. Thus, even in a high-risk population, the estimated sample size to detect a 50% decrease over 10 years between an *H pylori* eradicated versus noneradicated group would be more than 17,000 per group.[18] Ethical considerations provide another formidable barrier because, even though only a minority of individuals with *H pylori* will develop malignant complications, we are not able to definitively predict who will or will not progress; this line of reasoning forms the rationale for the recommendation of most major medical societies to universally eradicate *H pylori* when diagnosed. Thus, with-holding eradication treatment or providing a placebo treatment for a known carcinogen would be unethical.[17] Notably, in countries where *H pylori* eradication therapy is still not universally recommended, such as in South Korea, randomized controlled trials (RCTs) of *H pylori* eradication versus no eradication have continued to be conducted; these studies have provided risk reduction estimates in distinct high-risk populations, including those with family history of gastric cancer[19] or prior

history of gastric cancer[20,21] (discussed elsewhere in this article), although the ethics of these studies has been questioned. The same group that published these referenced studies is currently conducting an RCT of *H pylori* eradication therapy versus placebo to investigate the effect of *H pylori* eradication on gastric cancer incidence in the general population (HELPER study, NCT02112214); the anticipated completion date for this 10-year follow-up study is 2029.

Multiple retrospective cohort studies have been published, the majority in Asian-Pacific countries, analyzing the association between *H pylori* eradication treatment and primary prevention of gastric cancer.[22] Important differences across studies are those already listed elsewhere in this article, with the major differences including variability with respect to *H pylori* eradication regimens (most used clarithromycin-based regimens), rigor with respect to *H pylori* diagnosis determination, whether or not *H pylori* eradication confirmation testing was performed (and modality), reference groups, study time period, and duration and completeness of follow-up, as well as the baseline demographics of the cohort itself (eg, several studies had a greater than 70% male predominance, with variability in the mean age at study entry).[22] Moreover, most of these studies were not designed to separately analyze outcomes according to the presence or absence of symptoms or the presence or absence of gastric pathology, such as gastric or duodenal ulcers or already existing gastric (pre)neoplasia; or, this factor was analyzed in a limited fashion. Notwithstanding, a meta-analysis of cohort studies published before May 2015 demonstrated that *H pylori* eradication treatment was associated with a pooled 48% lower risk (incidence rate ratio, 0.52; 95% confidence interval [CI], 0.41–0.64) of incident gastric cancer, which was not significantly different compared with the pooled estimate for RCTs (incidence rate ratio, 0.60; 95% CI, 0.44–0.81) ($P = .34$ by meta-regression).[22] There was a trend toward greater benefit with a longer duration of follow-up after eradication ($P = .06$), but this difference was not statistically significant; the mean follow-up for the included studies ranged from 24 to 121 months. This meta-analysis also supported prior studies suggesting that the benefit of *H pylori* eradication for primary prevention is greater in populations with a higher gastric cancer incidence compared with a lower incidence. It should be emphasized, however, that this meta-analysis included only 2 studies conducted outside of the Asian-Pacific region, and one was conducted in Colombia,[23] a country with a high gastric cancer incidence; thus, only 1 study was from a country with a low to intermediate incidence of gastric cancer (Finland).[24] Of note, the Finnish study, which was conducted from 1986 to 1998, used a decrease in *H pylori* serum antibody titers as a surrogate for *H pylori* eradication, which may have led to misclassification.

Since the publication of that meta-analysis, 2 retrospective cohort studies from Western populations (Sweden, the United States) were published, both with different study designs.[25,26] The population-based retrospective cohort study from Sweden (2005–2012) compared the incidence of NCGA in patients who received *H pylori* eradication treatment to the general Swedish population as the reference group.[26] The majority of individuals were 18 to 59 years old, and the mean follow-up time for this study was only 3.7 years (maximum, 7.5 years; minimum not specified, but presumably 1 year). Details regarding the *H pylori* positivity rate in the general population comparator group, as well as the presence of symptoms or gastric pathology, and whether or not individuals had received *H pylori*

treatment before study entry were not available or provided in the study. The exposure group included patients with gastric pathology based on *International Classification of Disease* codes, including gastric ulcers, duodenal ulcers, and atrophic gastritis. Moreover, eradication confirmation testing was not universally performed after *H pylori* treatment and thus *H pylori* eradication cannot be confirmed in the primary exposure group; acknowledging this limitation, the authors did conduct a separate analysis among individuals who received more than 1 prescription of *H pylori* treatment during follow-up. Notwithstanding, after correction of an error in the statistical analysis,[27] the authors reported that, among 95,176 Swedish individuals who received *H pylori* eradication therapy, 0.1% (n = 69) developed NCGA over 351,018 person-years of follow-up time. The age- and sex-standardized risk of gastric cancer in the *H pylori* treated group compared with the general population decreased with increasing time since eradication therapy, such that the risk was 4.2-fold higher (95% CI, 3.04–5.66) and 3.1-fold higher (95% CI, 1.88–4.76) after 1 to 3 years and 3 to 5 years of follow-up, respectively. After 5 to 7.5 years of follow-up, however, the rate in the *H pylori* treated group was not significantly different compared with the general population (standardized incidence ratio, 2.06; 95% CI, 0.75–4.48); however, this finding was based on only 6 cases of NCGA.[27] There was a higher risk of NCGA among those with persistent *H pylori* infection, as indicated by at least 2 courses of eradication treatment during follow-up (standardized incidence ratio, 10.5; 95% CI, 3.82–22.8), compared with individuals who received only 1 course of *H pylori* treatment during follow-up (standardized incidence ratio, 2.38; 95% CI, 1.80–3.10).

One recently published retrospective cohort study conducted in United States veterans included a limited secondary analysis investigating the impact of *H pylori* eradication treatment among those with confirmed *H pylori* who also had subsequent *H pylori* testing to evaluate the success of treatment.[26] It was not stated whether patients were symptomatic or had known gastric (pre)neoplasia. Notably, only 2.2% of the starting cohort (n = 8020 of 371,813) had sufficient data available to be included in this secondary analysis. Based on this restricted sample of patients who had confirmatory testing, which is subject to bias, the authors did demonstrate that successful *H pylori* eradication was associated with a 76% lower likelihood (standardized hazard ratio, 0.24; 95% CI, 0.15–0.41) of distal gastric cancer compared with unsuccessful *H pylori* eradication. The follow-up time specifically for this subanalysis was not provided. Other methodological limitations need to be considered when interpreting the findings of this study[28]; for example, approximately 70% (n = 258,362 of 371,813) of the cohort were deemed to have *H pylori* exposure based solely on prescriptions for anti–*H pylori* therapy without confirmatory laboratory testing identified in the medical record.

Multiple RCTs have also been published that compare *H pylori* eradication versus no eradication and the subsequent incidence of gastric cancer, and thus complement the observational evidence provided from cohort studies. Unfortunately, there is a similar dearth of evidence from low or intermediate risk populations from Western countries. Recently, the Cochrane Gut Group updated their systematic review and meta-analysis, which was published in 2015, that compared the incidence of gastric cancer in asymptomatic individuals from the general population randomized to *H pylori* eradication therapy versus no therapy. Their comprehensive literature search through February 2, 2020, identified 7

distinct baseline RCTs (ie, no overlapping study populations) that met the full inclusion criteria. Six of these RCTs were performed in Asian countries, and the seventh was performed in Colombia.[19,23,29–34] No RCTs analyzing *H pylori* eradication versus no eradication on gastric cancer incidence have been conducted in countries with populations at low or intermediate risk for NCGA. Table 1 provides descriptions of these base RCTs, which resulted in a number of subsequent publications that are organized in the full Cochrane Review.[29] Based on meta-analysis of 8323 individuals in these 7 RCTs (modified intention to treat), compared with placebo or no treatment, *H pylori* eradication treatment was associated with a significant 46% lower risk (relative risk [RR], 0.46; 95% CI, 0.40–0.72) of incident gastric cancer on 4 to 22 years of follow-up time; the number needed to treat to have 1 person benefit was 72 (95% CI, 55–118). There was no significant heterogeneity observed across the studies. The quality of evidence was downgraded from high to moderate for this primary analysis based on a few important considerations. First, although 4 studies were deemed low risk of bias, 2 were deemed high risk and 1 was at unclear risk. Second, the *H pylori* eradication regimens used in these 7 studies varied; indeed, many of these studies started enrolling before 1994, which is when proton-pump inhibitors became more widely available. Last, some studies used a factorial design, with some arms including *H pylori* eradication therapy and vitamin supplementation, for example; as such, it was sometimes not possible to isolate fully whether the observed relative risk reduction in gastric cancer was wholly attributable to *H pylori* eradication. Based on meta-analysis of the 4 RCTs (n = 6301) that reported on gastric cancer-related mortality, randomization to *H pylori* eradication therapy versus no therapy/placebo was associated with a significant 49% lower risk of gastric-cancer related mortality (RR, 0.61; 95% CI, 0.40–0.92) on follow-up ranging from 7 to 22 years, with a number needed to treat to benefit of 137 (95% CI, 89–667).

Concomitant gastric preneoplasia

As described elsewhere in this article, one of the leading mechanisms underlying the chemopreventive effect of *H pylori* eradication treatment is that successful eradication of *H pylori* substantially decreases and ideally eliminates persistent inflammation. Indeed, the majority of individuals with *H pylori* nonatrophic gastritis and nonsevere atrophic gastritis will have normalization of these mucosal changes after successful *H pylori* eradication. The return of normal gastric mucosa also restores gastric acid production and facilitates the restoration of the normal gastric microbiota,[35] which likely also contributes to the beneficial effect of *H pylori* eradication in these early, reversible mucosal stages. However, if there are severe mucosal changes present, including severe gastric atrophy with or without gastric intestinal metaplasia, studies suggest that the benefit of *H pylori* eradication treatment, even with confirmed eradication of *H pylori* organisms, is attenuated and potentially even null. The presence of gastric intestinal metaplasia has been considered the first irreversible stage in the Correa cascade and the earliest point of no return, although a handful of cohort studies have challenged this notion of irreversibility.[36] Our understanding of the chemopreventive effects of *H pylori* eradication once preneoplastic gastric mucosal changes have developed is limited at best and largely reflects the difficulty in conducting robust clinical studies to investigate this question with rigor. As such, most studies have

included mixed populations with or without gastric preneoplastic changes—under which non-metaplastic and metaplastic gastric atrophy both qualify.

A few studies have provided some insight, however. The authors of the updated Cochrane meta-analysis of RCTs cited elsewhere in this article conducted a subgroup analysis of 3425 individuals who had gastric preneoplasia at baseline and demonstrated that there was no difference in gastric cancer incidence between those randomized to *H pylori* eradication treatment versus placebo or no treatment; 2.4% of participants randomized to treatment (42 of 1734 participants) compared with 3.4% of participants randomized to placebo or no treatment (57 of 1691 participants) developed gastric cancer on follow-up.[29] It should be noted, however, that the authors included dysplasia (grade not specified) as a preneoplastic mucosal change. A recent comprehensive systematic review with meta-analysis that was focused specifically on the natural history and outcomes of gastric intestinal metaplasia reported that, among individuals with confirmed gastric intestinal metaplasia and no higher grade pathology, *H pylori* eradication treatment versus placebo was associated with a 17% higher risk of progression (RR, 1.17; 95% CI, 1.01–1.36) to more advanced histology (moderate certainty in evidence), although the authors noted that the estimate was largely driven by data from 1 trial, the Shandong Interventional Trial.[33,36] This same trial though had conflicting results in another analysis, because *H pylori* eradication treatment in individuals with confirmed gastric intestinal metaplasia was also associated with regression to improved histology.[33,36,37] For the outcome of gastric cancer incidence specifically, *H pylori* eradication treatment versus placebo was associated with a significantly decreased risk in patients with or without gastric intestinal metaplasia (RR, 0.68; 95% CI, 0.48–0.96) on follow-up ranging from 4 to 16 years; however, when limited to only individuals with gastric intestinal metaplasia, there was similarly no substantial benefit on follow-up ranging from 5 to 12 years (RR, 0.76; 95% CI, 0.36–1.61).[17] Importantly, the data informing these meta-analyses were drawn primarily from 3 main RCTs, 2 from China and 1 from Colombia. The findings were somewhat driven by 1 large RCT from the Fujian Province, China with 7.5 years of follow-up; in this study, compared with placebo, the eradication of *H pylori* was associated with a decreased risk of gastric cancer only in individuals without precancerous lesions (atrophy, intestinal metaplasia, or dysplasia) at the outset, but there was no difference between the treatment and placebo groups when the analysis included individuals with precancerous lesions, including dysplasia.

Despite the conflicting evidence, *H pylori* eradication as chemoprevention for gastric cancer among individuals with gastric intestinal metaplasia (and other premalignant mucosal pathology) is still recommended by most international guidelines.[38–41] Because these individuals remain at risk of gastric cancer despite *H pylori* eradication, most international medical societies also suggest ongoing endoscopic surveillance for early detection of neoplasia, although the recommendations remain mixed in the absence of high-quality evidence derived from RCTs. Importantly, this finding underscores the need for more studies to better define mechanisms driving neoplastic progression in the absence of ongoing *H pylori* infection, such as the role of the non–*H pylori* microbiome and metabolites. Indeed, a better understanding of these mechanisms will help to inform the identification of adjunctive chemopreventive agents to ideally reverse these mucosal abnormalities and restore normal gastric mucosa, or at least halt further progression.

H pylori eradication for gastric cancer prevention in specific populations

Family history of gastric cancer.—*H pylori* and family history of gastric cancer are the 2 strongest risk factors for gastric cancer. Approximately 10% of gastric cancers demonstrate familial aggregation. Having a family history of gastric cancer in a first-degree relative compared with no family history is associated with an approximately 3-fold higher risk of gastric cancer, although this risk varies from 2-fold up to 10-fold higher in case-control studies, depending on the ethnic group and country of origin.[42] In addition to sharing genetics, family members share environmental exposures, behaviors, and cultural practices, as well as dietary habits and preferences. Furthermore, family members can share the same strains of *H pylori* as well as develop similar host immune responses to chronic *H pylori* infection; they may also have a greater susceptibility to infection.[43–47] To this end, studies have demonstrated that individuals who have a family history of gastric cancer more often have *H pylori* infection and more often demonstrate precancerous gastric mucosal changes that are more severe compared with individuals without a family history. Although there are guideline recommendations for endoscopic screening in individuals with a family history of gastric cancer in a first-degree family member, there is a notable dearth of studies analyzing strategies for chemoprevention in this high-risk population. One recent double-blind, placebo-controlled RCT from South Korea, in which 1838 first-degree relatives of individuals with gastric cancer were randomized to *H pylori* treatment versus placebo, demonstrated that *H pylori* eradication treatment was associated with a 55% decreased risk of incident gastric cancer (hazard ratio [HR], 0.45; 95% CI, 0.21–0.94) during a median follow-up of 9.2 years, based on the modified intention-to-treat analysis (n = 1676).[19] Gastric cancer occurred with significantly lower frequency in those with successful *H pylori* eradication compared with those with persistent infection (0.8% vs 2.9%; HR, 0.27; 95% CI, 0.10–0.70).[19] There is a relative consensus globally for recommending a test and treat strategy for *H pylori* as a chemopreventive measure among individuals with a positive family history of gastric cancer,[41,48] but recommendations are mixed in some Western countries, namely the United States,[49,50] owing to lack of high-quality evidence supporting this practice.

Metachronous gastric cancer (tertiary prevention).—To date, there have been at least 3 RCTs of *H pylori* eradication versus no eradication for reducing the risk of metachronous gastric cancer, with 2 studies[20,51] reporting a decreased risk of subsequent gastric cancer and a third study[52] demonstrating no statistically significant difference in the incidence of metachronous gastric cancer in those who were randomized to *H pylori* treatment versus no treatment ($P = .15$). Several observational studies have also been performed, with overall mixed results, either demonstrating a benefit or a null association, which likely reflects sample size considerations and significant differences in study design. Notably, no studies outside of Asia have investigated the effect of *H pylori* eradication for tertiary chemoprevention. A meta-analysis of 10 studies, including both RCTs and cohort studies that were published before May 2015, demonstrated that, compared with the reference group, *H pylori* eradication was associated with 54% lower risk of metachronous gastric cancer (RR, 0.46; 95% CI, 0.35–0.60).[22] The duration of follow-up for these studies ranged from a minimum of 24 months to a maximum of 58 months. A third RCT published in 2018 (and, thus, not included in the previously referenced meta-analysis) with median

follow-up of 5.9 years, reported that, compared with placebo, *H pylori* eradication therapy was associated with a significant 50% decrease in the risk of metachronous gastric cancer (HR, 0.50; 95% CI, 0.26–0.94) based on a modified intention-to-treat analysis; moreover, among individuals who had baseline atrophy of the corpus lesser curvature, those who received *H pylori* eradication treatment more often had improvement in atrophy grade at 3 years compared with individuals who received placebo (48.4% vs 15.0%; $P<.001$).[20]

These data, coupled with the observation that the vast majority of individuals with NCGA have background preneoplastic mucosal changes at diagnosis, provide further evidence for the field effect that occurs within the context of chronic *H pylori* exposure. Moreover, multiple studies in the past decade have confirmed that ongoing *H pylori* infection may lead to genome instability and aberrant gene expression as a result of *H pylori*–mediated epigenetic changes and dysregulated DNA repair, among other potentially carcinogenic events.[53] Taken together, these data do lend support to the strategy of treatment of *H pylori* in the presence of gastric premalignant mucosal changes. However, the extrapolation of these data outside of the populations included in these studies is problematic, given the variability in and interaction between host genetic risk and *H pylori* strain specific virulence that might characterize other diverse populations. Thus, although *H pylori* eradication therapy for tertiary prevention of gastric cancer seems reasonable, studies are needed across diverse populations, especially low to intermediate risk populations from Western countries.

Collectively, these data suggest there is insufficient evidence to support broad population-based testing and treatment of *H pylori* as a screening strategy in populations with a low incidence of gastric cancer, but this might be reasonable for higher risk populations, including those residing within countries that are overall low risk based on population aggregation.[48,54] Several questions remain when considering how to best translate the current evidence into clinical practice, particularly among high-risk populations residing in otherwise low-risk geographic regions; for example, determining the optimal age for *H pylori* screening and treatment because gastric premalignant changes are more frequent in older individuals who have greater cumulative *H pylori* exposure, as well as determining how to balance the desire for chemoprevention with the increasing rates of *H pylori* eradication failure and antibiotic resistance.

Aspirin and Nonsteroidal Anti-inflammatory Drugs as Chemoprevention Against Gastric Cancer

Aspirin and nonaspirin NSAIDs have both been investigated extensively for their role in cancer prevention, with their protective effect appearing most relevant for adenocarcinomas.[55] The daily intake of aspirin or nonaspirin NSAIDs has been associated with risk reductions of up to 63% in colorectal cancer and up to nearly 40% for breast, lung, and prostate adenocarcinomas. The exact molecular basis of this chemopreventive effect is not fully elucidated and likely varies depending on the cancer location, cancer phenotype, and individual characteristics, such as host genetic composition and environmental contributors. That said, several biologically plausible hypotheses have been proposed, the majority of which are COX dependent, although COX-independent pathways also seem to be relevant. NSAIDs, including aspirin, inhibit COX-1 and COX-2 production. The

inhibition of COX-2 seems to be most relevant in chemoprevention against malignancies of the gastrointestinal tract, namely, colorectal and (noncardia) gastric cancers. Several studies have consistently demonstrated that COX-2 levels are significantly higher in gastrointestinal malignancies; indeed, higher COX-2 expression is observed in gastric cancer tissue compared with tissue samples obtained from normal gastric mucosa in the same individual. This finding suggests a role for increased prostaglandin biosynthesis and COX-2 overexpression in carcinogenesis, as well as lymphovascular invasion and metastasis.[55] COX-2 is involved in several other pathways that, when dysregulated, are also implicated in carcinogenesis; these pathways include promotion of angiogenesis and cell proliferation, as well as inhibition of apoptosis. NSAIDs including aspirin, presumably through blockade of COX-2, have antitumor growth effects, including the inhibition of angiogenesis and the upregulation of mediators leading to apoptosis (eg, activation of caspase-3).[56–58] Aspirin and nonaspirin NSAIDs might also exert chemopreventive benefit through COX-independent pathways, including activation of nuclear factor-κB, activated protein 1, Wnt-ß-catenin, and extracellular signal-regulated kinase, among others.[59–62] Some of these pathways exert important roles in *H pylori*–induced gastric carcinogenesis, adding a further layer of complexity.

Numerous cohort and case control studies, along with several meta-analyses, analyzing the association between aspirin and nonaspirin NSAIDs and risk of gastric cancer, have been published to date. The results are generally consistent and demonstrate an inverse association between regular NSAID use and the risk of noncardia gastric cancer. Notably, the protective association for noncardia gastric cancer does seem to be driven more so by aspirin, with the data for nonaspirin NSAID use generally demonstrating a lesser risk attenuation or a null association. Again, these mixed findings may relate more to study design considerations such as rigor of the statistical analysis with respect to confounder adjustment and exposure misclassification, particularly because NSAIDs can be obtained over the counter in most countries. Many studies that analyzed nonaspirin NSAIDs did not adjust for aspirin use, which is important because some studies have demonstrated as high as 56% overlap between nonaspirin NSAID users and aspirin users.[63] At least 2 studies have analyzed the association according to histology of noncardia gastric cancer, both with congruent findings that the risk reduction was stronger for intestinal-type, compared with diffuse-type histology, which tends to have a greater genetic predisposition as opposed to the former, where environmental factors are key drivers.[63,64]

Most studies report a risk reduction for noncardia gastric cancer among regular aspirin users of approximately 20% to 50%, although these values vary depending on the definition of regular use (typically at least once weekly), the duration of use, the rigor of the analysis, the completeness of the data, and other population characteristics, including geography and *H pylori* status. One of the most recently published meta-analyses, which analyzed 33 studies from Asia, Europe, and North America and included nearly 2 million individuals, demonstrated that the use of aspirin at least monthly was associated with a 16% to 26% significantly lower risk of noncardia gastric cancer.[65] Based on a meta-analysis of 3 studies, aspirin use compared with nonuse was also associated with a significantly lower risk of gastric cancer-related mortality. Another recent meta-analysis of both any NSAID use, aspirin only, and nonaspirin NSAID use reported significant 30% (RR, 0.70; 95%

CI, 0.59–0.84), 36% (RR, 0.64; 95% CI, 0.53–0.78), and 26% (RR, 0.74; 95% CI, 0.60–0.93) respective reductions in the risk of noncardia gastric cancer; whereas, none were associated with cardia gastric cancer.[66] Subgroup analyses demonstrated consistent findings irrespective of study design (cohort vs case control).

Individual studies conducted in populations with a higher gastric cancer risk, including those conducted in Asia and among individuals with *H pylori* exposure, have generally demonstrated greater risk decreases with regular aspirin use versus nonuse. One large territory-wide study from Hong Kong, which included 63,605 individuals with *H pylori* infection who were successfully eradicated between 2003 and 2012, demonstrated that regular aspirin use (at least once weekly) compared with no use or infrequent use was associated with a significantly reduced risk of gastric cancer (HR, 0.30; 95% CI, 0.15–0.61) on follow-up out to a median of 7.6 years (interquartile range, 5.1–10.3 years). A greater decrease in risk was observed with increasing aspirin frequency, dose, and duration of use (all *P* trends <.001).[62] The risk reduction associated with aspirin doses of less than 100 mg was 62% (HR, 0.38; 95% CI, 0.18–0.79) versus 85% in users of aspirin 100 mg or higher (HR, 0.15; 95% CI, 0.03–0.65), although the CI was wider in the latter group owing to smaller sample size (n = 4607 [8%] vs 1725 [3%]). The mechanisms underlying the greater magnitude of risk reduction observed in this cohort of *H pylori* eradicated individuals compared with cohorts with mixed *H pylori* infected and uninfected individuals are not well defined. NSAID use has been demonstrated to decrease *H pylori* proliferation and enhance the antimicrobial effect of anti–*H pylori* treatment, as well as attenuate potential *H pylori*–induced carcinogenic pathways; indeed, *H pylori* infection is associated with increased prostaglandin synthesis and COX-2 expression, which might be blocked by NSAID consumption.[67–71] The chemopreventive benefit of NSAID use, especially aspirin, after *H pylori* has been eliminated, however, has been incompletely investigated. It is likely that many participants in the referenced study from Hong Kong[62] already had underlying gastric premalignant mucosal changes; whether regular NSAID use decreases the likelihood of malignant transformation, which is known to occur even after successful *H pylori* eradication,[36] is undetermined. Notably, 1 RCT of rofecoxib 25 mg/d versus placebo in individuals with histologically confirmed intestinal metaplasia and successful *H pylori* eradication reported no significant difference in the frequency of intestinal metaplasia regression or in the severity of intestinal metaplasia after 2 years of follow-up.[72] It is possible that NSAIDs, including aspirin, are more relevant with respect to the prevention of actual malignant transformation, as opposed to earlier phases of progression. This remains an important area of investigation because there are limited options for gastric cancer risk attenuation in this high-risk population, save perhaps interval endoscopic surveillance, which is costly and has limitations.

Although these data are overall promising, particularly for aspirin, evidence from RCTs is needed to guide positioning of NSAIDs as chemopreventive agents against gastric cancer. The most pressing knowledge gaps that need to be bridged include defining the high-risk populations who might benefit most from NSAID chemoprevention and in whom there is minimal harm; the minimum effective dose, frequency, and duration of use needed for benefit; and the ideal drug (eg, aspirin vs selective COX-2 inhibitors, such as celecoxib, which have fewer adverse gastrointestinal effects compared with nonselective agents), which

should also consider individual comorbidities (eg, cardiovascular risk, bleeding risk). To date, no RCTs have been conducted analyzing NSAID use and gastric cancer incidence or mortality as the primary outcome. One related RCT was conducted using the Women's Health Study cohort. In this study, nearly 40,000 women age 45 years or older who were generally healthy were randomly assigned to every other day aspirin 100 mg or placebo and were followed for the outcome of an invasive cancer diagnosis at any site. Over an average follow-up of 10 years, there was no significant association between aspirin use and the risk of invasive gastric cancer.[73] However, this study was likely underpowered for gastric cancer because only 20 cases occurred (cardia vs noncardia not specified); the population is also a low-risk population for gastric cancer, because the Women's Health Study recruited female health professionals and the overall demographic included less than 10% non-White races/ethnicities.[74] A secondary analysis of individual level data from 8 eligible RCTs where study participants were randomized to daily aspirin versus no aspirin and originally followed for the primary outcome of cardiovascular events, demonstrated the potential benefit of regular use of aspirin for chemoprevention and decreasing the risk of cancer-related mortality. Among 23,535 participants randomized to aspirin use, there was a lesser all-cancer mortality, including gastrointestinal cancers specifically (HR, 0.46; 95% CI, 0.27–0.77), after 5 years of follow-up. For cancers overall, the benefit was greater with longer duration of aspirin use, but aspirin doses in excess of 75 mg did not impact the risk estimates. For gastric adenocarcinoma specifically (cardia vs noncardia not specified), there was a lower risk of death only after 10 to 20 years of follow-up (HR, 042; 95% CI, 0.23–0.79). Competing risk of death is certainly a consideration in this study; the cancer incidence was not reported.

α-Difluoromethylornithine as Chemoprevention Against Gastric Cancer in Patients with Gastric Preneoplasia

Polyamines have been implicated in gastric carcinogenesis. These effectors, which are generated by ornithine deoxycarboxylase, have been associated with disruption of DNA repair mechanisms and inducing DNA damage, as well as altering the host immune response in gastric tissue. The expression of ornithine deoxycarboxylase in the gastric mucosa is part of the host innate immune response to *H pylori* infection.[75,76] Treatment with α-difluoromethylornithine (DFMO), which is an inhibitor of ornithine deoxycarboxylase, has been demonstrated to directly reduce *H pylori* virulence and attenuate risk of gastric dysplasia and carcinoma in Mongolian gerbils via a decrease in polyamine concentration in gastric tissue and abrogating polyamine-driven oxidative stress.[76] At least in experimental studies, DFMO also enhances DNA repair and decreases apoptosis-resistant cells with DNA damage; in this way, DFMO directly impacts genome stability in *H pylori*–infected gastric mucosa.[75–78] As such, DFMO has been proposed as a chemopreventive agent specifically in *H pylori*–associated gastric carcinogenesis and human trials are ongoing. Studies have demonstrated a chemopreventive effect of DFMO (in combination with sulindac) with respect to colorectal adenoma recurrence, which is hypothesized to be via a similar mechanism of polyamine inhibition.[79–81]

Other Chemopreventive Agents Against Gastric Cancer

Several other medications and dietary interventions have been investigated for their chemopreventive effects against gastric cancer, mostly with mixed findings and without high-quality data. Studies of nutritional intakes and cancer risk are inevitably difficult to conduct in a rigorous manner owing to the large sample sizes and long follow-up time that are needed, not to mention the challenges with respect to residual confounding, accurate exposure assessment, and determining the level of sustained dietary modification that is needed for an effect. This said, dietary interventions are attractive as chemoprevention, owing to the fact that they are generally safe, cost effective, and feasible. As such, certain dietary interventions might have an adjunctive role in addition to other lifestyle modifications that are known to decrease noncardia gastric cancer (as well as the risk of other cancer types). Dietary interventions include limiting the consumption of salted foods, high nitrite foods, processed foods, and red meats, and increasing the consumption of fresh vegetables and fruits, particularly citrus fruits and those high in beta-carotene, vitamin C, and antioxidants, and possibly garlic and allium vegetables. Garlic and its derivatives have antioxidant, antimicrobial, and immunomodulatory properties, among other benefits.[82] Studies have demonstrated that garlic is associated with a decreased risk of metachronous colorectal adenomas, and possibly also gastric cancer.[82–84] Calcium and magnesium might also have benefit in decreases noncardia gastric cancer risk.[85] Curcumin has been investigated in mechanistic studies, but clinical data are limited. Clinical and experimental data suggest a possible benefit of green tea and ginseng consumption.[86–90] Selenium, which is an essential trace element that is consumed in the diet, has also been investigated as a chemopreventive agent in gastric cancer given its antioxidant properties, in addition to anti-inflammatory, proapoptotic, and antiangiogenic properties.[91]

One RCT from Linqu County, Shandong Province of China randomly assigned 2258 *H pylori* seropositive individuals to *H pylori* treatment, vitamin supplementation, garlic supplementation, or placebo (2 × 2 × 2 factorial design) and 1107 *H pylori* seronegative individuals to vitamin supplementation, garlic supplementation, or placebo (2 × 2 factorial design). The vitamin supplementation intervention included the administration of vitamin C, vitamin E, and selenium for 7.3 years (1995–2003), whereas the garlic supplementation intervention included administration of garlic extract and oil over this same time period. Notably, *H pylori* treatment was amoxicillin 1 g and omeprazole 20 mg 2 times per day for 2 weeks and it is not stated whether or not nonserologic testing and confirmation of eradication was performed. The authors did report excellent compliance among participants. Based on 22 years of follow-up, *H pylori* treatment (odds ratio [OR], 0.48; 95% CI, 0.32–0.71), and vitamin supplementation (OR, 0.64; 95% CI, 0.46–0.91), but not garlic supplementation (OR, 0.81; 95% CI, 0.57–1.13) were associated with reduced incidence of gastric cancer. All 3 interventions, compared with placebo, were associated with a significantly decreased gastric cancer–related mortality; however, the effects of vitamin supplementation on gastric cancer incidence and garlic supplementation on mortality generally occurred later, and only after 14.7 years of follow-up. Separate analyses were not conducted for noncardia versus cardia, but the authors noted that the majority of gastric cancers were noncardia.[82] Other RCTs of dietary interventions with or without concomitant *H pylori* eradication treatment have been conducted in other high-risk populations.[23] The

coadministration of vitamins and antioxidants with *H pylori* eradication therapy does seem to have a greater chemopreventive effect compared with eradication treatment alone.[29] The factorial design of some of these trials, however, make it difficult to isolate the effect, if even present, of any singular exposure. Also complicating this field are the baseline risk of gastric cancer in the study population and the modifying effects of other environmental, cultural, and nongenetic factors, including nutritional deficiencies, as well as genetic factors; these factors limit generalizability. These findings do warrant exploration in other high-risk populations for the primary reasons stated elsewhere in this article—dietary modifications are generally safe, low-cost, and sustainable interventions that can be implemented on a larger scale, and might have other off-target benefits related to risk reduction of other disease pathology.

Metformin and statins have also been investigated clinically for their chemopreventive effects for gastric cancer based on supportive data from experimental studies. Metformin decreases gastric cancer cell viability, invasion, and migration via downregulation of COX expression, as well as through downregulation of hypoxia inducible factor 1a, pyruvate kinase M2, phosphatidylinositol 3-kinase/protein kinase b, and poly (ADP-ribose) polymerase expression.[92–95] By inhibiting phosphatidylinositol 3-kinase/protein kinase b and poly (ADP-ribose) polymerase pathways specifically, metformin also induces cell cycle arrest and apoptosis in gastric cancer cells. There are numerous observational studies, the majority of which are limited to individuals with type 2 diabetes (indication bias), which analyze the association between metformin and gastric cancer incidence. Collectively, the conclusions are mixed, with some studies, including large population-based studies, demonstrating null findings, whereas others demonstrate a protective effect.[96–101] These inconsistent data relate to significant differences in study design with respect to the study population, the rigor of the statistical analysis, including confounder adjustment and assessment of the exposure, such as new user versus prevalent user designs, as well as variable accounting of immortal time bias,[102] and preclude strong conclusions. Many studies did not adjust for relevant medications including aspirin, NSAIDs, statins, and insulin, or other relevant confounders such as *H pylori* exposure, smoking, and body mass index. One recent meta-analysis that included eligible cohort studies published through October 2019 demonstrated that using 8 cohort studies with approximately 1.2 million type 2 diabetics, metformin use was associated with 21% decrease in gastric cancer risk (HR, 0.79; 95% CI, 0.62–1.00); separate estimates were not provided for noncardia versus cardia gastric cancer.[96] Meta-analyses of the studies that analyzed sulfonylurea derivatives and noninsulin antidiabetic agents demonstrated a null association with gastric cancer incidence. Geographic differences seem to be relevant, because the magnitude of the protective association was amplified when meta-analysis was limited to the 3 studies from Asian populations only (HR, 0.54; 95% CI, 0.38–0.78), but the benefit was significantly attenuated when limited to the 5 studies from Western populations (HR, 0.99; 95% CI, 0.99–0.99). One recent cohort analysis conducted among diabetic patients from Hong Kong who were successfully eradicated for *H pylori* demonstrated that metformin use was associated with a significantly lower risk of gastric cancer compared with nonusers, and there was a trend toward an increased benefit with increasing duration and dose of metformin.[99] The authors

also conducted a propensity score adjustment, as well as repeated their analysis using time varying covariates and lag time analysis with similar findings.[102,103]

There is also biological plausibility underlying a hypothesized chemopreventive effect of statins for gastric cancer, but high-quality and consistent clinical data are lacking.[104,105] Well-conducted RCTs among specific high-risk populations are needed to adjudicate the findings presented herein regarding aspirin, NSAIDs, metformin, and statin use, among other putative chemopreventive agents to establish their effectiveness, or lack thereof, in noncardia gastric cancer. Despite otherwise promising data at least for aspirin and metformin, these cannot yet be recommended outside of their primary indications.

SUMMARY

There is ample evidence of the benefit of *H pylori* eradication in primary chemoprevention against intestinal-type noncardia gastric cancer when eradication occurs before the development of advanced preneoplastic mucosal changes. There might still be benefit thereafter, but the data are overall mixed and the benefit seems to be attenuated at best. Experimental as well as clinical data support other agents as primary chemoprevention, all with biological plausibility and the majority already used clinically for benign conditions. Although the largest body of evidence is available for NSAIDs, particularly aspirin, there are still no RCTs analyzing primary prevention of gastric cancer as the outcome. Dietary modifications as chemoprevention in gastric cancer also show promise and are particularly attractive given their favorable safety profile. Unfortunately, despite the substantial burden of gastric cancer globally, little progress has been made to rigorously analyze chemopreventive agents. To move the needle forward, the research agenda should ideally be focused on primary prevention trials, as well as on investigations aiming to personalize the selection of chemoprevention agents in high risk individuals. Several major knowledge gaps persist, including defining the role of agents, such as aspirin or metformin, as chemoprevention after *H pylori* eradication in individuals who have developed gastric preneoplasia, as well as identifying the age at which these interventions are most beneficial in specific populations. Another challenge remains in identifying effective chemoprevention for non-*H pylori*–associated gastric cancer. Focused investigation is needed in the face of an expanding aging population and the projected increase in gastric cancer-related deaths so that we can appropriately position gastric cancer chemopreventive agents in the armamentarium of gastric cancer control programs.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424. [PubMed: 30207593]

2. Anderson WF, Rabkin CS, Turner N, et al. The Changing Face of Noncardia Gastric Cancer Incidence Among US Non-Hispanic Whites. J Natl Cancer Inst 2018;110:608–15. [PubMed: 29361173]
3. Correa P, Piazuelo MB, Wilson KT. Pathology of gastric intestinal metaplasia: clinical implications. Am J Gastroenterol 2010;105:493–8. [PubMed: 20203636]
4. Correa P, Piazuelo MB. Helicobacter pylori infection and gastric adenocarcinoma. US Gastroenterol Hepatol Rev 2011;7:59–64. [PubMed: 21857882]
5. Nomura A, Stemmermann GN, Chyou PH, et al. Helicobacter pylori infection and gastric carcinoma among Japanese Americans in Hawaii. N Engl J Med 1991; 325:1132–6. [PubMed: 1891021]
6. Parsonnet J, Friedman GD, Vandersteen DP, et al. Helicobacter pylori infection and the risk of gastric carcinoma. N Engl J Med 1991;325:1127–31. [PubMed: 1891020]
7. Forman D, Newell DG, Fullerton F, et al. Association between infection with Helicobacter pylori and risk of gastric cancer: evidence from a prospective investigation. BMJ 1991;302:1302–5. [PubMed: 2059685]
8. Helicobacter and Cancer Collaborative Group. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut 2001;49:347–53. [PubMed: 11511555]
9. McColl KEL. Clinical practice. Helicobacter pylori infection. N Engl J Med 2010; 362:1597–604. [PubMed: 20427808]
10. Hooi JKY, Lai WY, Ng WK, et al. Global Prevalence of Helicobacter pylori Infection: systematic Review and Meta-Analysis. Gastroenterology 2017;153:420–9. [PubMed: 28456631]
11. Plummer M, Franceschi S, Vignat J, et al. Global burden of gastric cancer attributable to Helicobacter pylori. Int J Cancer 2015;136:487–90. [PubMed: 24889903]
12. Nozaki K, Shimizu N, Inada K, et al. Synergistic promoting effects of Helicobacter pylori infection and high-salt diet on gastric carcinogenesis in Mongolian gerbils. Jpn J Cancer Res 2002;93:1083–9. [PubMed: 12417037]
13. Cao X, Tsukamoto T, Seki T, et al. 4-Vinyl-2,6-dimethoxyphenol (canolol) suppresses oxidative stress and gastric carcinogenesis in Helicobacter pylori-infected carcinogen-treated Mongolian gerbils. Int J Cancer 2008;122:1445–54. [PubMed: 18059022]
14. Cao D, Jiang J, Tsukamoto T, et al. Canolol inhibits gastric tumors initiation and progression through COX-2/PGE2 pathway in K19-C2mE transgenic mice. PLoS One 2015;10:e0120938. [PubMed: 25781635]
15. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983;1:1273–5. [PubMed: 6134060]
16. Kuipers EJ, Uyterlinde AM, Peña AS, et al. Long-term sequelae of Helicobacter pylori gastritis. Lancet 1995;345:1525–8. [PubMed: 7791437]
17. Graham DY, Asaka M. RE: Effects of helicobacter pylori treatment on gastric cancer incidence and mortality in subgroups. J Natl Cancer Inst 2014;106. 10.1093/jnci/dju352.
18. Graham DY, Shiotani A. The time to eradicate gastric cancer is now. Gut 2005; 54:735–8. [PubMed: 15888771]
19. Choi IJ, Kim CG, Lee JY, et al. Family history of gastric cancer and helicobacter pylori treatment. N Engl J Med 2020;382:427–36. [PubMed: 31995688]
20. 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. [PubMed: 29562147]
21. Cho SJ, Choi IJ, Kook MC, et al. Randomised clinical trial: the effects of Helicobacter pylori eradication on glandular atrophy and intestinal metaplasia after subtotal gastrectomy for gastric cancer. Aliment Pharmacol Ther 2013;38: 477–89. [PubMed: 23822578]
22. Lee Y-C, Chiang T-H, Chou C-K, et al. Association between helicobacter pylori eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology 2016;150:1113–24.e5. [PubMed: 26836587]
23. Correa P, Fontham ET, Bravo JC, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. J Natl Cancer Inst 2000;92:1881–8. [PubMed: 11106679]

24. Kosunen TU, Pukkala E, Sarna S, et al. Gastric cancers in Finnish patients after cure of Helicobacter pylori infection: a cohort study. Int J Cancer 2011;128: 433–9. [PubMed: 20309944]
25. Doorakkers E, Lagergren J, Engstrand L, et al. Helicobacter pylori eradication treatment and the risk of gastric adenocarcinoma in a Western population. Gut 2018;67:2092–6. [PubMed: 29382776]
26. Kumar S, Metz DC, Ellenberg S, et al. Risk factors and incidence of gastric cancer after detection of helicobacter pylori infection: a large cohort study. Gastroenterology 2020;158:527–36.e7. [PubMed: 31654635]
27. Doorakkers E, Lagergren J, Engstrand L, et al. Reply to: Helicobacter pylori eradication treatment and the risk of gastric adenocarcinoma in a western population. Gut 2020;69:1149–50. [PubMed: 31113849]
28. Shah SC. Practice update: risk factors and incidence of gastric cancer after detection of helicobacter pylori infection. J Scan Pract Update 2019. Available at: https://www.practiceupdate.com/content/risk-factors-and-incidence-of-gastric-cancer-after-detection-of-helicobacter-pylori-infection/91600/65/9/1. Accessed November 6, 2020.
29. Ford AC, Yuan Y, Forman D, et al. Helicobacter pylori eradication for the prevention of gastric neoplasia. Cochrane Database Syst Rev 2020;7:CD005583. [PubMed: 32628791]
30. Wong BCY, Zhang L, Ma J, et al. Effects of selective COX-2 inhibitor and Helicobacter pylori eradication on precancerous gastric lesions. Gut 2012;61: 812–8. [PubMed: 21917649]
31. Saito D, Boku N, Fujioka T, et al. Impact of H-pylori eradication on gastric cancer prevention: endoscopic results of the Japanese intervention trial (JITHP-study). A Randomized multi-center trial. Gastroenterology 2005.
32. Wong BC-Y, Lam SK, Wong WM, et al. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004;291:187–94. [PubMed: 14722144]
33. You W, Brown LM, Zhang L, et al. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. J Natl Cancer Inst 2006;98:974–83. [PubMed: 16849680]
34. Leung WK, Lin SR, Ching JYL, et al. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on Helicobacter pylori eradication. Gut 2004;53:1244–9. [PubMed: 15306578]
35. Noto JM, Peek RM. The gastric microbiome, its interaction with Helicobacter pylori, and its potential role in the progression to stomach cancer. PLoS Pathog 2017;13:e1006573. [PubMed: 28982167]
36. Gawron AJ, Shah SC, Altayar O, et al. AGA technical review on gastric intestinal metaplasia-natural history and clinical outcomes. Gastroenterology 2020;158: 705–31.e5. [PubMed: 31816300]
37. Li W-Q, Ma J-L, Zhang L, et al. Effects of Helicobacter pylori treatment on gastric cancer incidence and mortality in subgroups. J Natl Cancer Inst 2014; 106. 10.1093/jnci/dju116.
38. Gupta S, Li D, El Serag HB, et al. AGA clinical practice guidelines on management of gastric intestinal metaplasia. Gastroenterology 2020;158:693–702. [PubMed: 31816298]
39. Pimentel-Nunes P, Libânio D, Marcos-Pinto R, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Micro-biota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy 2019;51:365–88. [PubMed: 30841008]
40. Banks M, Graham D, Jansen M, et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. Gut 2019;68:1545–75. [PubMed: 31278206]
41. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut 2015;64:1353–67. [PubMed: 26187502]
42. Yaghoobi M, Bijarchi R, Narod SA. Family history and the risk of gastric cancer. Br J Cancer 2010;102:237–42. [PubMed: 19888225]

43. Shin CM, Kim N, Yang HJ, et al. Stomach cancer risk in gastric cancer relatives: interaction between Helicobacter pylori infection and family history of gastric cancer for the risk of stomach cancer. J Clin Gastroenterol 2010;44:e34–9. [PubMed: 19561529]
44. Chang Y-W, Han Y-S, Lee D-K, et al. Role of Helicobacter pylori infection among offspring or siblings of gastric cancer patients. Int J Cancer 2002;101:469–74. [PubMed: 12216076]
45. Nam JH, Choi IJ, Cho S-J, et al. Helicobacter pylori infection and histological changes in siblings of young gastric cancer patients. J Gastroenterol Hepatol 2011;26:1157–63. [PubMed: 21392104]
46. Brenner H, Bode G, Boeing H. Helicobacter pylori infection among offspring of patients with stomach cancer. Gastroenterology 2000;118:31–5. [PubMed: 10611151]
47. El-Omar EM, Oien K, Murray LS, et al. Increased prevalence of precancerous changes in relatives of gastric cancer patients: critical role of H. pylori. Gastroenterology 2000;118:22–30. [PubMed: 10611150]
48. 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. [PubMed: 27707777]
49. El-Serag HB, Kao JY, Kanwal F, et al. Houston consensus conference on testing for Helicobacter pylori Infection in the United States. Clin Gastroenterol Hepatol 2018;16:992–1002.e6. [PubMed: 29559361]
50. Chey WD, Leontiadis GI, Howden CW, et al. ACG clinical guideline: treatment of Helicobacter pylori infection. Am J Gastroenterol 2017;112:212–39. [PubMed: 28071659]
51. Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 2008; 372:392–7. [PubMed: 18675689]
52. Choi J, Kim SG, Yoon H, et al. Eradication of Helicobacter pylori after endoscopic resection of gastric tumors does not reduce incidence of metachronous gastric carcinoma. Clin Gastroenterol Hepatol 2014;12:793–800.e1. [PubMed: 24100112]
53. Hanada K, Graham DY. Helicobacter pylori and the molecular pathogenesis of intestinal-type gastric carcinoma. Expert Rev Anticancer Ther 2014;14:947–54. [PubMed: 24802804]
54. Fock KM, Katelaris P, Sugano K, et al. Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection. J Gastroenterol Hepatol 2009;24: 1587–600. [PubMed: 19788600]
55. Harris RE, Beebe-Donk J, Doss H, et al. Aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade (review). Oncol Rep 2005;13:559–83. [PubMed: 15756426]
56. Wang WH, Huang JQ, Zheng GF, et al. Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. J Natl Cancer Inst 2003;95:1784–91. [PubMed: 14652240]
57. Wong BC, Zhu GH, Lam SK. Aspirin induced apoptosis in gastric cancer cells. Biomed Pharmacother 1999;53:315–8. [PubMed: 10472431]
58. Jiang X-H, Lam S-K, Lin MCM, et al. Novel target for induction of apoptosis by cyclo-oxygenase-2 inhibitor SC-236 through a protein kinase C-beta(1)-dependent pathway. Oncogene 2002;21:6113–22. [PubMed: 12203123]
59. Wu C-Y, Wu M-S, Kuo KN, et al. Effective reduction of gastric cancer risk with regular use of nonsteroidal anti-inflammatory drugs in Helicobacter pylori-infected patients. J Clin Oncol 2010;28:2952–7. [PubMed: 20479409]
60. Yamamoto Y, Yin MJ, Lin KM, et al. Sulindac inhibits activation of the NF-kappaB pathway. J Biol Chem 1999;274:27307–14. [PubMed: 10480951]
61. Cuzick J, Otto F, Baron JA, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol 2009;10:501–7. [PubMed: 19410194]
62. Cheung KS, Chan EW, Wong AYS, et al. Aspirin and risk of gastric cancer after helicobacter pylori eradication: a territory-wide study. J Natl Cancer Inst 2018; 110:743–9. [PubMed: 29361002]
63. Epplein M, Nomura AMY, Wilkens LR, et al. Nonsteroidal antiinflammatory drugs and risk of gastric adenocarcinoma: the multiethnic cohort study. Am J Epidemiol 2009;170:507–14. [PubMed: 19584132]

64. Akre K, Ekström AM, Signorello LB, et al. Aspirin and risk for gastric cancer: a population-based case-control study in Sweden. Br J Cancer 2001;84:965–8. [PubMed: 11286478]
65. Niikura R, Hirata Y, Hayakawa Y, et al. Effect of aspirin use on gastric cancer incidence and survival: a systematic review and meta-analysis. JGH Open 2020;4:117–25. [PubMed: 32280753]
66. Huang X-Z, Chen Y, Wu J, et al. Aspirin and non-steroidal anti-inflammatory drugs use reduce gastric cancer risk: a dose-response meta-analysis. Oncotarget 2017;8:4781–95. [PubMed: 27902474]
67. Hudson N, Balsitis M, Filipowicz F, et al. Effect of Helicobacter pylori colonisation on gastric mucosal eicosanoid synthesis in patients taking non-steroidal anti-inflammatory drugs. Gut 1993;34:748–51. [PubMed: 8314505]
68. Takahashi M, Katayama Y, Takada H, et al. The effect of NSAIDs and a COX-2 specific inhibitor on Helicobacter pylori-induced PGE2 and HGF in human gastric fibroblasts. Aliment Pharmacol Ther 2000;14(Suppl 1):44–9. [PubMed: 10807402]
69. Wang WH, Wong WM, Dailidiene D, et al. Aspirin inhibits the growth of Helicobacter pylori and enhances its susceptibility to antimicrobial agents. Gut 2003; 52:490–5. [PubMed: 12631656]
70. Chang SH, Chung JG, Huang LJ, et al. Ibuprofen affects arylamine N-acetyltransferase activity in Helicobacter pylori from peptic ulcer patients. J Appl Toxicol 1998;18:179–85. [PubMed: 9685046]
71. Lee C-W, Rickman B, Rogers AB, et al. Combination of sulindac and antimicrobial eradication of Helicobacter pylori prevents progression of gastric cancer in hypergastrinemic INS-GAS mice. Cancer Res 2009;69:8166–74. [PubMed: 19826057]
72. Leung WK, Ng EKW, Chan FKL, et al. Effects of long-term rofecoxib on gastric intestinal metaplasia: results of a randomized controlled trial. Clin Cancer Res 2006;12:4766–72. [PubMed: 16899628]
73. Cook NR, Lee I-M, Gaziano JM, et al. Low-Dose Aspirin in the Primary Prevention of Cancer. JAMA 2005;294:47. [PubMed: 15998890]
74. Available at: whs.bwh.harvard.edu/images/WHS website-Overview of study.pdf. Accessed November 3, 2020.
75. Hardbower DM, Asim M, Luis PB, et al. Ornithine decarboxylase regulates M1 macrophage activation and mucosal inflammation via histone modifications. Proc Natl Acad Sci U S A 2017;114:E751–60. [PubMed: 28096401]
76. Chaturvedi R, de Sablet T, Asim M, et al. Increased Helicobacter pylori-associated gastric cancer risk in the Andean region of Colombia is mediated by spermine oxidase. Oncogene 2015;34:3429–40. [PubMed: 25174398]
77. Sierra JC, Suarez G, Piazuelo MB, et al. α-Difluoromethylornithine reduces gastric carcinogenesis by causing mutations in Helicobacter pylori cagY. Proc Natl Acad Sci U S A 2019;116:5077–85. [PubMed: 30804204]
78. Barry DP, Asim M, Leiman DA, et al. Difluoromethylornithine is a novel inhibitor of Helicobacter pylori growth, CagA translocation, and interleukin-8 induction. PLoS One 2011;6:e17510. [PubMed: 21386987]
79. Zell JA, Lin BS, Madson N, et al. Role of obesity in a randomized placebo-controlled trial of difluoromethylornithine (DFMO) + sulindac for the prevention of sporadic colorectal adenomas. Cancer Causes Control 2012;23:1739–44. [PubMed: 22907422]
80. Thompson PA, Wertheim BC, Zell JA, et al. Levels of rectal mucosal polyamines and prostaglandin E2 predict ability of DFMO and sulindac to prevent colorectal adenoma. Gastroenterology 2010;139:797–805, 805.e1. [PubMed: 20538001]
81. Raj KP, Zell JA, Rock CL, et al. Role of dietary polyamines in a phase III clinical trial of difluoromethylornithine (DFMO) and sulindac for prevention of sporadic colorectal adenomas. Br J Cancer 2013;108:512–8. [PubMed: 23340449]
82. Li W-Q, Zhang J-Y, Ma J-L, et al. Effects of Helicobacter pylori treatment and vitamin and garlic supplementation on gastric cancer incidence and mortality: follow-up of a randomized intervention trial. BMJ 2019;366:l5016. [PubMed: 31511230]
83. Tanaka S, Haruma K, Kunihiro M, et al. Effects of aged garlic extract (AGE) on colorectal adenomas: a double-blinded study. Hiroshima J Med Sci 2004;53: 39–45. [PubMed: 15726891]

84. Li H, Li H, Wang Y, et al. An intervention study to prevent gastric cancer by micro-selenium and large dose of allitridum. Chin Med J 2004;117:1155–60. [PubMed: 15361287]
85. Shah SC, Dai Q, Zhu X, et al. Associations between calcium and magnesium intake and the risk of incident gastric cancer: a prospective cohort analysis of the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study. Int J Cancer 2019. 10.1002/ijc.32659.
86. Tsukamoto T, Nakagawa M, Kiriyama Y, et al. Prevention of gastric cancer: eradication of helicobacter pylori and beyond. Int J Mol Sci 2017;18. 10.3390/ijms18081699.
87. Yang C, Du W, Yang D. Inhibition of green tea polyphenol EGCG((-)-epigallocatechin-3-gallate) on the proliferation of gastric cancer cells by suppressing canonical wnt/β-catenin signalling pathway. Int J Food Sci Nutr 2016;67:818–27. [PubMed: 27338284]
88. Shibata K, Moriyama M, Fukushima T, et al. Green tea consumption and chronic atrophic gastritis: a cross-sectional study in a green tea production village. J Epidemiol 2000;10:310–6. [PubMed: 11059513]
89. Inoue M, Tajima K, Hirose K, et al. Tea and coffee consumption and the risk of digestive tract cancers: data from a comparative case-referent study in Japan. Cancer Causes Control 1998;9:209–16. [PubMed: 9578298]
90. Kamangar F, Gao Y-T, Shu X-O, et al. Ginseng intake and gastric cancer risk in the Shanghai Women's Health Study cohort. Cancer Epidemiol Biomarkers Prev 2007;16:629–30. [PubMed: 17372265]
91. Steevens J, van den Brandt PA, Goldbohm RA, et al. Selenium status and the risk of esophageal and gastric cancer subtypes: the Netherlands cohort study. Gastroenterology 2010;138:1704–13. [PubMed: 20006613]
92. Chen G, Feng W, Zhang S, et al. Metformin inhibits gastric cancer via the inhibition of HIF1α/PKM2 signaling. Am J Cancer Res 2015;5:1423–34. [PubMed: 26101707]
93. Kato K, Gong J, Iwama H, et al. The antidiabetic drug metformin inhibits gastric cancer cell proliferation in vitro and in vivo. Mol Cancer Ther 2012;11:549–60. [PubMed: 22222629]
94. Courtois S, Durán RV, Giraud J, et al. Metformin targets gastric cancer stem cells. Eur J Cancer 2017;84:193–201. [PubMed: 28822889]
95. Yu G, Fang W, Xia T, et al. Metformin potentiates rapamycin and cisplatin in gastric cancer in mice. Oncotarget 2015;6:12748–62. [PubMed: 25909163]
96. Shuai Y, Li C, Zhou X. The effect of metformin on gastric cancer in patients with type 2 diabetes: a systematic review and meta-analysis. Clin Transl Oncol 2020; 22:1580–90. [PubMed: 32060719]
97. Zhang J, Wen L, Zhou Q, et al. Preventative and therapeutic effects of metformin in gastric cancer: a new contribution of an old friend. Cancer Manag Res 2020; 12:8545–54. [PubMed: 32982447]
98. Zhou X-L, Xue W-H, Ding X-F, et al. Association between metformin and the risk of gastric cancer in patients with type 2 diabetes mellitus: a meta-analysis of cohort studies. Oncotarget 2017;8:55622–31. [PubMed: 28903449]
99. Cheung KS, Chan EW, Wong AYS, et al. Metformin use and gastric cancer risk in diabetic patients after helicobacter pylori eradication. J Natl Cancer Inst 2019; 111:484–9. [PubMed: 30329127]
100. Murff HJ, Roumie CL, Greevy RA, et al. Metformin use and incidence cancer risk: evidence for a selective protective effect against liver cancer. Cancer Causes Control 2018;29:823–32. [PubMed: 30022336]
101. Zheng J, Xie S-H, Santoni G, et al. Metformin use and risk of gastric adenocarcinoma in a Swedish population-based cohort study. Br J Cancer 2019;121: 877–82. [PubMed: 31591459]
102. Khosrow-Khavar F, Kurteva S, Douros A. RE: metformin use and gastric cancer risk in diabetic patients after helicobacter pylori eradication. J Natl Cancer Inst 2019;111:1107–8. [PubMed: 31020327]
103. Cheung KS, Leung WK. Response to Khosrow-Khavar, Kurteva, and Douros. J Natl Cancer Inst 2019;111:1109. [PubMed: 31020323]
104. Kuoppala J, Lamminpää A, Pukkala E. Statins and cancer: a systematic review and meta-analysis. Eur J Cancer 2008;44:2122–32. [PubMed: 18707867]
105. Browning DRL, Martin RM. Statins and risk of cancer: a systematic review and metaanalysis. Int J Cancer 2007;120:833–43. [PubMed: 17131313]

106. Correa P, Fontham ETH, Bravo JC, et al. RESPONSE: Re: chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-Helicobacter pylori therapy. JNCI J Natl Cancer Inst 2001;93:559–60. [PubMed: 11287457]

107. 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 2018;67:1239–46. [PubMed: 28647684]

108. Zhou L, Lin S, Ding S, et al. Relationship of Helicobacter pylori eradication with gastric cancer and gastric mucosal histological changes: a 10-year follow-up study. Chin Med J 2014;127:1454–8. [PubMed: 24762588]

KEY POINTS

- *Helicobacter pylori* eradication remains the mainstay form of chemoprevention against noncardia gastric adenocarcinoma.
- However, the observations that the incidence of non-*H. pylori* associated gastric cancer is rising, and gastric cancer still develops in people after *H. pylori* eradication highlights the importance of investigations defining other effective chemopreventive agents.
- To date, many agents including aspirin, non-steroidal anti-inflammatory drugs, metformin, statins, and alpha-difluoromethylornithine have been investigated in their role as chemopreventive agents in gastric cancer.
- Future randomized controlled clinical trials particularly for high-risk populations, such as people with gastric preneoplastic mucosal changes are needed in order to provide guidance on how to position the use of these agents for gastric cancer prevention.

CLINICS CARE POINTS

- Several randomized controlled trials have confirmed that chemoprevention through *H. pylori* eradication is associated with a reduced risk of noncardia gastric adenocarcinoma; however, the chemopreventive benefit is significantly attenuated in patients who have already developed gastric premalignant mucosal changes.
- Additional studies are especially needed to define underlying mechanisms of neoplastic progression following *H. pylori* eradication and in patients without *H. pylori* to help target discovery of chemoprevention agents.
- Several case-control and cohort studies support an association between aspirin and potentially non-aspirin non-steroidal anti-inflammatory drugs and noncardia gastric cancer.
- This review describes the current literature surrounding several posited chemopreventive agents for gastric cancer, and provides a critical appraisal of the current evidence.

Table 1

RCTs evaluating the association between *H pylori* eradication and gastric cancer

First Author, Publication year	Country/ Region	Study Population	Intervention		Follow-up	Outcome Measures	
Choi et al,[19] 2020	Korea, single center	Participants with a family history of gastric cancer, n = 1826 randomized (n = 1587 evaluated for *H pylori* eradication)	**1** **2**	Lansoprazole 30 mg, Amoxicillin 1g, Clarithromycin 500 mg BID × 7 d Placebo × 7 d *H pylori* eradication = 70.1%	Median duration of follow-up was 9.2 y (IQR, 6.2–10.6) and 10.2 y (IQR, 8.9–11.6) for incident gastric cancer and overall survival, respectively	**1** **2** **3**	Incident gastric cancer Overall survival Incident gastric adenoma
Correa et al[23] 2000 Correa et al,[106] 2001	Colombia, 2 communities in Narino Province	Participants with confirmed histologic diagnoses of gastric preneoplasia, n = 976 randomized (n = 852 in intention to treat; n = 631 complete case analyses); age 29–69, mean 51.1 y; 46.1% male	**1** **2**	Bismuth 262 mg, amoxicillin 500 mg, metronidazole 375 mg TID × 14 d • With or without dietary supplements Placebo • With or without dietary supplements *H pylori* eradication rate = 58.0%	Cited analysis, 6 y. *Note: multiple points of follow-up have been published to date, with the most recent a 16-y analysis.*[107]	**1** **2**	Progression of preneoplastic lesions (based on histologic score, and global assessment). • Gastric cancer outcome published separately[108] Relative risk of progression, no change, regression of histologic lesions
Leung et al,[34] 2004	China, 11 villages in Yantai County, Shandong Province	Participants with vs without dyspepsia, who underwent upper endoscopy with biopsy. n = 587 randomized (34% with gastric preneoplasia at baseline); age 35–75 y, mean, 52.0 y; 47.8% male *Note: 33.7% with preneoplasia at baseline*	**1** **2**	Omeprazole 20 mg, amoxicillin 1g, clarithromycin 500 mg BID × 7 d Placebo × 7 d *H pylori* eradication rate = 55.6%	Cited analysis, 5 y *Note: 10-y follow-up also published.*[108]	**1**	Histologic outcomes at 2 and 5 y (subsequently, 8 and 10 y)
Saito et al 2005 (abstract only; full study not published as of Feb. 2020)	Japan, 145 centers	Participants were healthy volunteers with *H pylori* infection. n = 629 randomized; age 20–59 y, mean not reported	**1** **2**	Lansoprazole 30 mg, amoxicillin 1.5 g, clarithromycin 400 mg once daily × 7 d No eradication *H pylori* eradication rate = 74.4%	Follow-up stated as "≥4y"	**1**	Histologic regression or progression of atrophy by at least 1 grade (*Note: did not report on gastric cancer incidence, although this was a priori planned outcome*)
Wong 2004[32]	China, 7 villages in Changle Country, Fujian Province	Participants undergoing screening endoscopy (age 35–65 y, mean 42.2 y). n = 2423 evaluated, and n = 1628 with *H pylori* infection but without endoscopic lesions (eg, peptic ulcer) were randomized *Note: 37.7% with*	**1** **2**	Omeprazole 20 mg, amoxicillin/ clavulanic acid 750 mg, metronidazole 400 mg BID × 14 d Placebo × 14 d *H pylori* eradication rate = 83.7%	Follow-up time, 7.5 y	**1** **2**	Incidence of gastric cancer Incidence in those with vs without premalignant lesions

First Author, Publication year	Country/ Region	Study Population	Intervention	Follow-up	Outcome Measures
		premalignant lesions at baseline (gastric atrophy, intestinal metaplasia, gastric cancer)			
Wong et al,[30] 2012	China, 12 villages Linqu County, Shandong Province	Participants with *H pylori* infection and advanced gastric lesions (severe chronic atrophy, intestinal metaplasia, dysplasia); age 35–64 y, mean 53 y n = 1024 randomized, 2 × 2 factorial design *ALL participants had premalignant lesions at baseline*	**1** Omeprazole 20 mg, amoxicillin 1g, clarithromycin 500 mg BID × 7 d **a.** PLUS placebo BID, OR **b.** PLUS celecoxib **2** Placebo **3** Celecoxib + placebo *H pylori* eradication rate = 63.5%	Follow-up time, 5 y	**1** Gastric cancer **2** Regression or progression of gastric premalignant lesions
You et al,[33] 2006	China, 13 villages Linqu County, Shandong Province	Participants were selected randomly and underwent upper endoscopy, n = 2258 participants randomized; age 35–64 y, mean 46.8 y 2 × 2 × 2 factorial design *Note:* H pylori *confirmed via serologic testing* *64% had preneoplastic lesions at baseline*	**1** Omeprazole 20 mg, Amoxicillin 1g BID × 14 d a. with or without vitamin or garlic supplementation **2** Placebo ± vitamin or garlic supplementation • “Vitamins” = vitamin C, E, selenium • Garlic = garlic oil and Kyolic aged garlic extract	Follow-up time, 14.7 y *Note: multiple points of follow-up have been published to date, with the most recent a 22-y analysis.*[82]	**1** Prevalence of dysplasia or gastric cancer **2** Prevalence of other precancerous lesions (severe chronic atrophic gastritis, intestinal metaplasia) **3** Average ‘severity’ score

Abbreviation: BID, 2 times per day; IQR, interquartile range; TID, 3 times per day.

Data from Refs.[19,23,29,30,32–34,82,106–108]