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Review Article

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# Current Evidence for a Paradigm Shift in Gastric Cancer Prevention From Endoscopic Screening to *Helicobacter pylori* Eradication in Korea

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## ABSTRACT

Gastric cancer is prevalent in Korea and ranked as the third most common cancer in 2019, followed by lung and thyroid cancers. The National Cancer Screening Program (NCSP) for gastric cancer has been implemented in adults aged ≥40 since 1999 and involves endoscopic screening every 2 years. The beneficial effects of the current NCSP on early cancer detection, cost-effectiveness, and mortality reduction are evident. However, the screening program results in a large socioeconomic burden and the consumption of medical resources, as it focuses solely on secondary prevention (early detection) rather than primary prevention of cancer. *Helicobacter pylori* is defined as a group I carcinogen by the International Agency for Research on Cancer. Hence, its eradication has been suggested as an important primary gastric cancer prevention strategy. Well-designed randomized controlled trials involving high-risk groups (post-endoscopic resection of early gastric cancer and family history of gastric cancer) and long-term follow-up studies in the general population have provided high-quality evidence regarding the effects of *H. pylori* eradication on gastric cancer prevention. In this review, we discussed the evidences for a possible modification of the current gastric cancer secondary prevention strategy by introducing primary prevention through *H. pylori* eradication. Areas for future research to optimize primary prevention strategies were also suggested.

**Keywords:** Gastric cancer; Endoscopy; *Helicobacter pylori*; Atrophy

## INTRODUCTION

In Korea, cancer was the leading cause of death in 2019 (81,203 deaths, comprising 27.5% of all deaths) [1]. Gastric cancer was the most frequently diagnosed cancer annually until 2018 and ranked third in 2019, followed by thyroid and lung cancers [1,2]. Furthermore, the number of new cases diagnosed in 2019 was 29,493, which was not significantly different from previous years [2].

The National Cancer Screening Program (NCSP) for gastric cancer was initiated in 1999 by medical aid beneficiaries to reduce gastric cancer mortality through early detection and treatment [3]. In addition, the program was expanded to provide endoscopy or upper

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gastrointestinal series (UGIS) every 2 years for adults aged ≥40 years [3,4]. The beneficial effects of the NCSP are evident, especially with increasing early detection rates and reducing gastric cancer mortality [5,6]. However, the main limitation of the current NCSP for gastric cancer is that it focuses only on secondary prevention (early detection), which requires many resources.

*Helicobacter pylori (H. pylori)* is declared a group I carcinogen by the International Agency for Research on Cancer. Hence, its eradication has been suggested as an important primary gastric cancer prevention strategy. Well-designed randomized controlled trials (RCTs) involving high-risk groups (post-endoscopic resection of early gastric cancer (EGC) and family history of gastric cancer) and recently reported long-term follow-up results from RCTs conducted in the general population provided evidence of the effect of *H. pylori* eradication on gastric cancer prevention. In this narrative review, we discussed the evidences for future modification of the current gastric cancer secondary prevention strategy by including the primary prevention of *H. pylori* eradication and suggested future research areas including risk stratification strategies.

## GASTRIC CANCER EPIDEMIOLOGY AND THE CURRENT STATUS OF THE NCSP IN KOREA

The annual number of newly diagnosed gastric cancer cases in Korea has been approximately 30,000 since 2009 [7]. The age-standardized rate (ASR) of gastric cancer incidence was 45.6/100,000 cases in 1999 and decreased to 30.8/100,000 cases in 2019. The mortality rate of gastric cancer was the highest of all cancers in 1999 (ASR, 23.8/100,000 cases); however, the ASR of gastric cancer mortality in 2019 was 7.1/100,000 cases, making gastric cancer the fourth leading cause of cancer-related death, followed by lung, liver, and colorectal cancers [1]. The 5-year relative survival rate was 77.5% between 2015 and 2019 compared with 43.9% between 1993 and 1995 (33.6% increase) [7]. According to the Surveillance, Epidemiology, and End Results (SEER) stage categories, gastric cancer stage distributions were 64.3% for localized, 10.9% for regional, and 10.9% for distant in 2019, with prognosis worsening as the stages increase (5-year relative survival, localized 97.0%; regional 62.1%; distant 6.4%) [7].

The NCSP provides endoscopy or UGIS every 2 years for adults aged ≥40 years. The NCSP participation rate for gastric cancer increased from 7.4% in 2002 to 62.9% in 2019 [8,9], and the lifetime screening (participating in the NCSP at least once or more) rate increased from 52.0% in 2004 to 85.5% in 2018 [10]. According to the new guidelines for gastric cancer screening released in 2015 [4], endoscopy is the primary screening modality. The UGIS is recommended as a screening modality for participants who cannot undergo endoscopy. The widespread use of image-enhanced endoscopy techniques has helped to detect EGCs [11,12]. There was a sharp increase in the rate of endoscopy from 31.2% in 2002 to 89.1% in 2019 [8,9].

## EFFECTIVENESS OF THE NCSP FOR GASTRIC CANCER

The effectiveness of gastric cancer screening in reducing mortality has been reported (**Table 1**) [6,13]. A nested case-control study using data from the NCSP showed that gastric cancer mortality decreased by 21% (odds ratio [OR], 0.79; 95% confidence interval [CI], 0.77–0.81) among screened individuals compared with those who had never been screened [6]. In a subgroup analysis, gastric cancer mortality reduction was significant only among patients


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**Table 1.** The effects of gastric cancer screening on mortality reduction in Korea

| Study (year) | Design | Database source | Entry year for screening | Follow-up periods | Sample size | Adjusted or matched variables | Screening modality | Overall mortality* | Gastric cancer mortality |
|---|---|---|---|---|---|---|---|---|---|
| Jun et al. [6]. (2017) | Nested case-control | Korean National Cancer Screening Program | 2002–2003 | 2004–2012 | Case 54,418; control 217,672 (1:4 matching) | Year of entry, age, sex, socioeconomic status | All | OR, 0.83 (95% CI, 0.81–0.85) | OR, 0.79 (95% CI, 0.77–0.81) |
| | | | | | | | EGD | OR, 0.61 (95% CI, 0.58–0.63) | OR, 0.53 (95% CI, 0.51–0.56) |
| | | | | | | | UGIS | OR, 1.00 (95% CI, 0.97–1.02) | OR, 0.98 (95% CI, 0.95–1.01) |
| Kim et al. [13]. (2018) | Prospective cohort | Four community-based cohorts | 1993–2004 | 1993–2014 | Unscreened 6,553; Screened 4,356 | Age, sex, *H. pylori* infection, smoking, alcohol drinking status | EGD | HR, 0.87 (95% CI, 0.79–0.95) | HR, 0.58 (95% CI, 0.36–0.94) |
| | | | | | | | UGIS | HR, 0.84 (95% CI, 0.70–1.00) | HR, 0.91 (95% CI, 0.36–2.33) |

OR = odds ratio; CI = confidential interval; EGD = esophagogastroduodenoscopy; UGIS = upper gastrointestinal series; *H. pylori* = *Helicobacter pylori*; HR = hazard ratio.
*OR HR in participants who had been screened compared to those who had never been screened.

who underwent endoscopy (OR, 0.53; 95% CI, 0.51–0.56), whereas no significant reduction was observed in those who underwent UGIS (OR, 0.98; 95% CI, 0.95–1.01). Furthermore, among those who underwent endoscopy, gastric cancer mortality reduction increased as the number of endoscopies increased (OR for once, 0.60; 95% CI, 0.57–0.63; OR for twice, 0.32; 95% CI, 0.28–0.37; OR for 3 times or more, 0.19; 95% CI, 0.14–0.26) [6]. Based on these results, UGIS has not been recommended by the NCSP as a primary screening modality for gastric cancer since 2018. Another cohort study, including participants from 4 Korean geographic areas, reported that those who underwent endoscopic gastric cancer screening had a 42% reduction in gastric cancer mortality compared with unscreened participants [13].

A similar effect was observed for esophageal cancer mortality rates due to the NCSP for gastric cancer. A cohort study using the NCSP database showed that esophageal cancer mortality significantly decreased by 50% in participants who underwent endoscopic screening (adjusted hazard ratio [HR], 0.50; 95% CI, 0.46–0.53) [14].

The increased detection rate of early-stage gastric cancer is a favorable effect of the NCSP. In a cohort study comprising 19,168 gastric cancer patients, those who underwent endoscopic screening were significantly more likely to be diagnosed with localized SEER stage cancer compared with never-screened (adjusted OR in endoscopy-screened patients, 2.10; 95% CI, 1.90–2.33) and UGIS-screened patients (adjusted OR in endoscopy-screened patients, 1.71; 95% CI, 1.55–1.89) [5]. Another study, including 18,414 individuals who participated in the NCSP, evaluated the effects of repeated endoscopic screening on the early detection of gastric cancer [15]. Participants who underwent repeated endoscopic screenings within 2 years had significantly higher EGC diagnoses (96% vs. 71%; P=0.01) and were more frequently treated with endoscopic resection for diagnosed cancer (54% vs. 23%; P=0.007) than those who did not undergo endoscopic screening within 2 years [15]. According to a nationwide survey data from the Korean Gastric Cancer Association, the prevalence of EGC increased from 28.6% in 2009 to 63.6% in 2019 among patients with surgically treated gastric cancer [16].

Adverse events associated with endoscopy include bleeding, perforation, infection associated with endoscopic devices, and adverse events associated with sedation [17,18]. A nationwide survey comprising 2,128,207 diagnostic endoscopic procedures from 50 hospitals revealed that the incidences of bleeding and perforation were 0.012% and 0.001%, respectively [17]. The NCSP for gastric cancer using endoscopy is associated with low adverse events, which are tolerable considering the benefits of screening.


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## ENDOSCOPIC SCREENING AND SURVEILLANCE GUIDELINES AMONG DIFFERENT GEOGRAPHIC REGIONS

Endoscopic gastric cancer screening is recommended every 2 years without risk stratification in Korea. However, whether 2 years is the optimal screening interval for prevention remains unclear. Several retrospective Korean studies have evaluated endoscopic screening intervals regarding mortality risk and advanced gastric cancer detection. Choi et al. [19] reported that newly diagnosed gastric cancer patients with 1–2 years endoscopy intervals had a significantly higher proportion of EGC (82.7% vs. 71.9%; P=0.002) and endoscopic resection treatment (33.8% vs. 24.7%; P=0.026) than those with 2–3 years interval. Nonetheless, significantly lower overall mortality risks were observed in patients with 1–2 years (adjusted HR, 0.45; 95% CI, 0.32–0.64) and 2–3 years endoscopy intervals (adjusted HR, 0.57; 95% CI, 0.33–0.98) when compared with those with no previous endoscopic screening. Park et al. [20] showed similar rates of endoscopically treated gastric neoplasms (adenoma or EGC) (51.5% vs. 50.0%, respectively) and advanced gastric cancer diagnoses in the 2 years and 3 years endoscopy interval groups. In another study, Nam et al. [21] showed that endoscopic surveillance intervals of 2 years (age- and sex-adjusted OR, 1.11; 95% CI, 0.75–1.64) and 3 years (age- and sex-adjusted OR, 1.21; 95% CI, 0.75–1.97) were not associated with increased detection of advanced gastric cancer when compared with 1-year intervals. These results collectively suggest that the current 2-year interval of the NCSP might be increased to 3 years without a significant increase in the gastric cancer mortality rate.

Gastric cancer screening for the general population is recommended in Korea and Japan, where gastric cancer incidence is high [4,22]. However, endoscopic screening is not recommended in other parts of the world, and surveillance is limited to patients with precancerous lesions, including atrophic gastritis and intestinal metaplasia (IM) [23-26]. **Table 2** summarizes the international endoscopic surveillance recommendations from published guidelines and consensus statements. The guidelines recommend assessing the severity and extent of atrophy or IM using biopsies from the antrum and corpus, endoscopy with imaging enhancement techniques, or serological tests to determine the necessity of endoscopic surveillance. In addition, evaluations of patient risk factors for gastric cancer, including a family history of gastric cancer and *H. pylori* status, are required. These guidelines recommend endoscopic surveillance every 3 years for patients with advanced atrophy or IM, whereas no endoscopic surveillance is recommended for those without risk factors, advanced atrophy, or IM. However, the evidence level of these recommendations was low, highlighting the need for large-scale prospective studies with cost-effective analyses to determine the optimal endoscopy surveillance intervals according to patient gastric cancer risk (*H. pylori* status, atrophy/IM, and family history of gastric cancer).

## *H. PYLORI* TREATMENT FOR METACHRONOUS GASTRIC CANCER PREVENTION

EGCs presumed to have minimal lymph node (LN) metastasis risk are indicated for endoscopic resection rather than conventional surgical gastrectomy combined with LN dissection [27,28]. Metachronous gastric cancer frequently develops after endoscopic resection, which preserves most gastric mucosa, with advanced mucosal atrophy or IM. A large retrospective Japanese study reported an annual incidence of metachronous gastric cancer development of approximately 3% [29]. Patients with EGC could be the most suitable


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**Table 2.** International endoscopic surveillance recommendations according to atrophic gastritis status were obtained from the guidelines and consensus statements

| Guidelines | Year | Patients' condition | Surveillance recommendations |
|---|---|---|---|
| Korean [4] | 2015 | · Adults aged ≥40 yr | Endoscopy every 2 yr as part of the national cancer screening program |
| Japanese [22] | 2014 | · Adults aged ≥50 yr | Endoscopy every 2 yr as part of the national cancer screening program |
| European [23] | 2019 | · Mild to moderate atrophy only in the antrum, no IM | No surveillance |
| | | · IM only in the antrum or only in the corpus without any risk factor (family history of gastric cancer, incomplete IM, autoimmune gastritis, or persistent *H. pylori* infection) | No surveillance |
| | | · IM only in the antrum or only in the corpus with a risk factor | Endoscopy every 3 yr |
| | | · Advanced stages of atrophic gastritis or IM in both antrum and corpus (OLGA or OLGIM stage III/IV) without a family history | Endoscopy every 3 yr |
| | | · Advanced stages of atrophic gastritis or IM in both antrum and corpus with a family history of gastric cancer | Endoscopy every 1–2 yr |
| British [24] | 2019 | · Atrophy or IM is limited to the antrum without risk factors (family history of gastric cancer or persistent *H. pylori* infection) | No surveillance |
| | | · Atrophy or IM limited to the antrum with risk factors | Endoscopy every 3 yr |
| | | · Extensive atrophy or IM affecting the antrum and corpus evaluated by Sydney protocol biopsies (antrum, angle, corpus lesser, and greater curvature) | Endoscopy every 3 yr |
| Teipei global consensus [25] | 2020 | · Advanced atrophy or IM after *H. pylori* eradication | Endoscopy every 2–3 yr |
| AGA Clinical practice [26] | 2021 | · Advanced atrophic gastritis (affecting the antrum and corpus, OLGA or OLGIM stage III/IV) | Endoscopy every 3 yr |

IM = intestinal metaplasia; *H. pylori* = *Helicobacter pylori*; OLGA = Operative Link for Gastritis Assessment; OLGIM = Operative Link for Gastric Intestinal Metaplasia assessment; AGA = American Gastroenterological Association.

candidates for clinical trials to prove whether *H. pylori* treatment reduces the risk of gastric cancer. To date, 3 RCTs have been conducted in Japan and Korea.

The first landmark multicenter study was published in 2008 by a Japanese group [30]. Fukase et al. [30] reported a multicenter, open-label, randomized study showing that new gastric cancer was diagnosed in 9 patients in the *H. pylori* eradication group (n=272) and 24 patients in a control group (n=272). The OR for metachronous gastric cancer was 0.353 (P=0.009). However, this study has several limitations. First, the maximum follow-up duration was 3 years, which was too short to adequately evaluate the gastric cancer prevention effects of *H. pylori* treatment. The newly detected gastric cancers within 1-year of endoscopic resection were most likely missed synchronous but erroneously included as metachronous gastric cancer outcomes. Second, the open-label design rendered the study vulnerable to biases, such as detection (i.e., bias in cancer detection) or attrition biases (i.e., selective follow-up loss). Third, no long-term follow-up results were reported.

In contrast, Choi et al. [31] reported the opposite conclusion from an open-label, single-center study (n=901) conducted at Seoul National University Hospital. The study showed no significant metachronous gastric cancer risk reduction during a median follow-up of 3 years (10/444 in the eradication group vs. 17/457 in the control group). However, this study had almost the same limitations as the previous study. Nonetheless, longer follow-ups, with a median of 71.6 months, revealed 18 metachronous gastric cancer cases in the eradication group compared with 36 cases in the control group. The difference in prevalence was statistically significant, with an HR of 2.02 (P=0.02) [32].

The benefit of *H. pylori* eradication therapy was demonstrated in a study conducted at the National Cancer Center in Korea [33]. Advantageously, this was a double-blinded, placebo-controlled, randomized trial with a longer follow-up duration (median 5.9 years, ranging from 3–13 years). Metachronous gastric cancer occurred in 7.2% (14/194) of patients in the


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treatment group and 13.4% (27/202) in the placebo group. The HR for the treatment group was 0.5, indicating a 50% reduction in gastric cancer risk. In addition, the HR for gastric cancer development was reduced to 0.32 in the *H. pylori* eradicated group (5.4%, 9/167) than in the *H. pylori* persistent group (14.0%, 32/228).

A meta-analysis including the 3 RCTs mentioned above showed that the risk ratio of new gastric cancer development after endoscopic resection was 0.49 (95% CI, 0.34–0.70). Furthermore, the number needed to treat (NNT) was 21 (95% CI, 16–36). These results emphasize the benefit of *H. pylori* treatment even for relatively old patients with advanced atrophic changes in the gastric mucosa [34].

Meanwhile, evidence is lacking regarding the preventive role of *H. pylori* treatment in preventing gastric cancer from occurring in the remnant stomach after partial gastrectomy. A double-blind placebo-controlled randomized trial evaluated the effect of *H. pylori* treatment on the improvement of atrophy and IM in patients who underwent distal gastrectomy [35]. At the 3-year follow-up after *H. pylori* treatment, *H. pylori* eradicated patients had improved atrophy and IM scores at the corpus of the remnant stomach than *H. pylori* persistent patients [35]. However, no difference was found in metachronous cancer development according to *H. pylori* treatment (3.4% [3/87] in the treatment group vs. 1.2% [1/82]) in the placebo group; P=0.378 by the log-rank test) during the median follow-up of 5 years [35]. In the longer follow-up period of this study (median 9.4 years), no additional metachronous gastric cancer had occurred since the primary study [36]. The role of *H. pylori* treatment in preventing gastric cancer was evaluated as a secondary outcome, but the study power was insufficient to confirm this outcome. Therefore, further studies are needed; however, these studies are difficult to conduct in Korea because the National Health Insurance Services has approved *H. pylori* treatment in gastric cancer patients who underwent gastrectomy since 2018.

## EVIDENCE FROM FIRST-DEGREE RELATIVES OF GASTRIC CANCER PATIENTS

A first-degree relative family history of gastric cancer increases the risk of development by 2–3 times compared with cases with no family history. Family members may share genetic susceptibility and important environmental risk factors, including *H. pylori* infection and dietary factors such as high salt intake, low socioeconomic status, and smoking or drinking habits [37]. Among these, the most attributable risk factor is *H. pylori* infection. Observational studies have revealed that *H. pylori* infection rates are higher among relatives of patients with gastric cancer and gastric mucosal atrophy of higher severity [38,39]. Since no intervention trial has been reported yet, the Maastricht V European guidelines recommend *H. pylori* treatment for those with a family history of gastric cancer. In contrast, the American College of Gastroenterology guidelines for North America did not recommend screening or treatment, both of which were published in 2017 [40,41].

In 2020, our group reported a well-designed, long-term intervention trial that demonstrated the benefit of *H. pylori* eradication for gastric cancer prevention in this high-risk group for the first time [42]. This study included 1,676 individuals with a first-degree family history of gastric cancer. During a median follow-up of 9.2 years, gastric cancer was detected in 1.2% (10/832) of the treatment group versus 2.7% (23/844) of the placebo group (HR, 0.45; 95% CI, 0.21–0.94). However, *H. pylori* infection persisted in approximately 30% of patients in the


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treatment group, potentially due to antibiotic resistance. In an additional analysis of those with successful *H. pylori* eradication, *H. pylori* treatment for gastric cancer prevention was more prominent, with a lower HR of 0.27 (95% CI, 0.10–0.70). This finding emphasizes that testing for successful *H. pylori* eradication should be performed after treatment to ensure maximum gastric cancer prevention.

## EVIDENCE FROM GENERAL POPULATION STUDIES

*H. pylori* infection is a well-known risk factor for gastric cancer; however, it remains unknown whether *H. pylori* treatment in asymptomatic healthy individuals can reduce the risk of gastric cancer. In Taiwan, a long-term cohort study was conducted in the Matsu Islands, where the incidence of gastric cancer is high. The mass eradication of *H. pylori* in over 7,000 residents began in 2004, and the participants were followed up until 2018 [43]. Compared with gastric cancer incidence between 1995 and 2003, *H. pylori* treatment effectively reduced the prevalence of gastric cancer by 53% (95% CI 30%–69%, P<0.001).

A recent systematic review and meta-analysis were conducted using 6 healthy general population studies and our study on the high-risk population of first-degree relatives of patients with gastric cancer [34]. This study showed that *H. pylori* eradication reduced the incidence of gastric cancer (relative risk 0.54, 95% CI 0.40–0.72) with a NNT of 72 (95% CI, 56–119). Among the 6 general population studies, 5 were from Eastern Asia (1 from Japan and 4 from China) and one from Columbia, all of which had high gastric cancer incidences. However, only 3 studies, including our gastric cancer first-degree relative study and 2 from China, had a low risk of bias, with a sample size >1,000.

The first general population study of low-risk bias was a prospective, randomized, placebo-controlled trial conducted in the Fujian province of China in 1994. This study recruited 1,630 asymptomatic *H. pylori*-infected participants. The initial primary outcome of a 7.5-year follow-up was reported in 2004 when no significant difference in gastric cancer incidence was found (11/813 in the placebo group vs. 7/817 in the treatment group, P=0.33) [44]. The participants were followed up for a total of 26.5 years. During this period, gastric cancer was diagnosed in 21 (2.57%) patients in the treatment group and 35 (4.31%) in the placebo group [45]. This long-term follow-up showed a significant reduction in gastric cancer risk among the treated asymptomatic patients (HR 0.57, 95% CI 0.33–0.98). However, this study had some limitations. First, only 3 endoscopic follow-ups were performed during the 26.5-year study period. Second, the study could not show a significant reduction in gastric cancer mortality due to the small sample size or missing values.

The second study with low-risk bias was the Shandong Intervention Trial conducted in Linqu County, China. This study had a 2×2×2 factorial design consisting of 3 interventions: *H. pylori* treatment, antioxidants (garlic extracts), and vitamins, with corresponding placebos. During the initial 7.3-year follow-up, *H. pylori* treatment did not show a significant risk reduction in gastric cancer, whereas a longer follow-up of 22.3 years revealed a significant reduction in gastric cancer risk of approximately 50% (OR 0.48, 95% CI 0.32–0.71) [46,47]. Gastric cancer mortality was also significantly reduced (OR 0.62, 95% CI 0.39–0.99). Furthermore, gastric cancer incidence was reduced by vitamin supplementation but not by garlic extracts. Interestingly, gastric cancer mortality was significantly reduced by all 3 interventions. However, a major limitation of this study was that the *H. pylori* treatment regimen was


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a dual therapy (amoxicillin and proton pump inhibitor), and secondary treatment after eradication failure was the same regimen. The eradication rate in the treatment group was 62% after the initial treatment and 73% after repeated treatment in cases of eradication failure [46]. During the 7.3-year follow-up, only 46% of the treatment group remained *H. pylori*-negative, suggesting that over 50% of the eradication group had a persistent infection or early reinfection. Thus, the 22.3-year long-term effect might be compromised because of this discrepancy between the allocated groups and actual *H. pylori* infection status during the follow-up period.

## ONGOING CLINICAL TRIALS IN THE GENERAL POPULATION

Two well-designed, ongoing, and large intervention trials will overcome the limitations of previous studies. The first has been ongoing since 2011 in Linqu County, China [48]. This study screened over 180,000 individuals aged 25–54 from March 2011 to September 2013. *H. pylori*-infected individuals were randomized, and the infection rate in this study population was 57.6%. Ten-day bismuth quadruple therapy (bismuth, omeprazole, tetracycline, and metronidazole) was administered to the *H. pylori* treatment group, and low-dose bismuth and omeprazole therapy was administered to the control group. The primary endpoint of the study was the incidence of gastric cancer, which was designed to detect a 20% decrease in gastric cancer incidence. Despite the limitations of cluster randomization based on the village, but not on each individual, and the use of low-dose therapy rather than true placebos, the large sample size of this trial will provide solid evidence for *H. pylori* eradication for gastric cancer prevention.

Another study involves a multicenter, randomized, controlled trial that has been ongoing in Korea since 2014 (ClinicalTrias.gov Identifier: NCT02112214) [49]. This study aimed to evaluate whether *H. pylori* treatment decreases the risk of gastric cancer in the general population. This study recruited individuals aged 40–65 years who agreed to participate in endoscopy surveillance every 2 years under the NCSP for gastric cancer in Korea. Screening and randomization were completed in early 2020, and follow-up will continue until 2029. The treatment consisted of bismuth quadruple therapy or a placebo for ten days. In addition to the primary outcome, *H. pylori* uninfected participants at the screening evaluation will also be followed up to determine whether the gastric cancer risk in the treatment group can be lowered to the same level as that of *H. pylori* uninfected participants.

## *H. PYLORI* TREATMENT AND GASTRIC CANCER RISK REDUCTION IN ATROPHIC GASTRITIS

Usually, *H. pylori* infection occurs in childhood and persists for a lifetime if not treated. Persistent infections spanning decades will most likely lead to precancerous changes in glandular atrophy and IM. There is a concept of "point-of-no-return," which suggests that *H. pylori* treatment is not effective for the regression of atrophy and/or gastric cancer prevention after a certain point of damage. However, some challenging results have been published suggesting that *H. pylori* treatment is still effective in reducing gastric cancer risk, even after severe atrophic changes have already developed.


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A recent systematic review and meta-analysis reported that atrophic gastritis and IM improved following *H. pylori* treatment (atrophic gastritis: OR 2.61, 95% CI 1.41–4.81, P=0.002; IM: OR 2.61, 95% CI 1.66–4.11, P<0.0001) [50]. However, whether the reversibility of histological changes in these diseases is associated with a risk reduction of gastric cancer is unknown [51,52].

Two large, general population, randomized, controlled trials reported inconsistent conclusions regarding whether *H. pylori* treatment after a precancerous change has already developed can reduce the risk of gastric cancer. A general population study from Linqu County in China with a 26.5-year follow-up reported subgroup analysis data according to the presence of premalignant gastric lesions, including chronic atrophic gastritis, IM, or dysplasia [45]. The adjusted HR for gastric cancer incidence was 0.37 (95% CI 0.15–0.95) for participants without premalignant lesions and 0.75 (95% CI 0.38–1.49) for those with premalignant lesions. These data suggest that *H. pylori* treatment is only effective before the development of premalignant lesions. In contrast, 22.3-year follow-up data from the Shandong Intervention Trial showed that *H. pylori* eradication significantly reduced gastric cancer only in the older age group over 55 years and in those who had advanced premalignant histological changes [47].

Most EGC patients have advanced premalignant histological changes. Our clinical trial evaluating the effect of *H. pylori* eradication on metachronous gastric cancer prevention showed baseline moderate-to-marked histologic atrophic changes in 80% and same-grade IM in 55% of the study participants at the corpus lesser curvature side of the stomach [33]. Because this study confirmed a definite gastric cancer prevention effect of *H. pylori* treatment despite underlying severe histological changes, it may be possible to apply this finding to the general population with severe histological changes. However, this indirect evidence should be confirmed by prospective studies conducted in the general population with well-defined baseline histological data.

## GASTRIC CANCER RISK ASSESSMENT BY ATROPHY EVALUATION

Atrophic gastritis is a well-known risk factor for gastric cancer. Therefore, accurate and reproducible assessment methods for risk stratification based on this factor are essential. The 3 most commonly used methods are serology tests for pepsinogen I/II, endoscopic, and histological assessments.

The pepsinogen test is a serological test that does not require endoscopy or biopsy. A serum pepsinogen I (sPG I) level of <70 mg/mL and a sPG I/II ratio of <3 are commonly accepted criteria for severe atrophic changes in the gastric mucosa. It is an easy, non-invasive method; however, it has some limitations in relation to the different reference values among commercial test kits. Moreover, *H. pylori* infection status, age, sex, smoking, alcohol intake, dietary habits, and hormone levels might affect the test results [53,54].

Endoscopic assessment using the Kimura–Takemoto classification is another non-invasive method for evaluating gastric atrophy [55]. Varying degrees of endoscopic experience among endoscopists affect atrophy evaluation agreement rates owing to its subjective nature. Consequently, interobserver variation was high, especially among inexperienced endoscopists. Presumably, agreement rates could improve after training [56,57].


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Histological assessment may be the gold standard for the evaluation of gastric atrophy. The updated Sydney system recommends obtaining biopsy specimens from 5 different locations of the gastric mucosa (from the lesser and greater curvature of the antrum, incisura angularis, and corpus lesser and greater curvature) [58]. A visual analog scale for atrophy or IM grading was used as a reference. Nonetheless, one study showed that interobserver agreement was quite low, even among Korean gastrointestinal pathologists, especially for atrophy (kappa value=0.19 for atrophy, 0.52 for IM). However, the interobserver agreement can be improved after consensus meetings among participating pathologists [59].

The operative link for gastritis assessment (OLGA) and operative link on gastric intestinal metaplasia assessment (OLGIM) have been suggested to quantify gastric cancer risk using histologic data from the updated Sydney system [60,61]. High-risk stages (i.e., OLGA stage III–IV or OLGIM stage III–IV) for gastric cancer development were associated with intestinal-type gastric cancer but not with diffuse-type gastric cancer [62]. In the Korean population, the proportion of high-risk OLGA stages was low at 6.9% before the age of 40 but gradually increased to 23%, 29.1%, and 41.1% for those in their 40s, 50s, and 60s, respectively [63]. A prospective study involving 1,755 patients in Italy showed that OLGA stages III and IV could reliably predict gastric cancer development [64].

Among the 3 atrophy assessment methods, the most appropriate in terms of accuracy and cost-effectiveness should be determined and applied for high-risk group selection within the general population.

## FUTURE PERSPECTIVE FOR GASTRIC CANCER SCREENING

Screening is recommended only for high-risk groups or by different screening intervals according to the participants' cancer risk in lung, colorectal, or liver cancer. However, in gastric cancer, *H. pylori* infection and atrophy are 2 major factors that can be applied to risk stratification. In Korea, most patients with gastric cancer have current or past *H. pylori* infections [65]. However, the current NCSP for gastric cancer only recommends 2-year interval endoscopy screening without risk stratification. This policy may result in the exhaustion of medical resources, unnecessary socioeconomic burdens, or problems associated with overdiagnosis.

The following areas of research need to be addressed to modify the current recommendations of the Korean NCSP and provide a more effective and efficient screening program:

First, gastric cancer incidence and mortality reduction should be addressed using *H. pylori* eradication therapy in the general population. Then, a primary prevention strategy should be incorporated into the current NCSP secondary prevention strategies.

Second, the effects of atrophy and IM on subsequent gastric cancer risk after *H. pylori* eradication should be assessed, including identification of the most appropriate test methods for *H. pylori* infection and atrophy that can classify populations according to risk.

Third, the differential effect of *H. pylori* infection and atrophy according to the histological type of gastric cancer should be determined. Intestinal and diffuse types of gastric cancer have different clinicopathological characteristics that may affect the parameters of screening


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programs, such as onset/termination age, intervals of endoscopy screening, and high-risk group definitions.

Fourth, family history, the second most important risk factor for gastric cancer development. Thus, the exact magnitude of risk in the absence or presence of *H. pylori* infection should be addressed.

Fifth, the early onset of gastric cancer before the age of 40 is also associated with *H. pylori* infection. If these cancers are mostly associated with *H. pylori* infection, then *H. pylori* infection screening using a non-invasive method at the age of 20 or 30 should be considered at the population level.

Finally, the economic burden of *H. pylori* infection testing and eradication therapy should be estimated. In addition, the adverse effects of *H. pylori* eradication should be monitored, including the unexplained overall mortality increase identified in a meta-analysis of RCTs [66].

The endoscopic gastric cancer screening program is already well established, with evident beneficial effects in reducing the gastric cancer burden in Korea. Further refinement of secondary screening programs that incorporate gastric cancer risk factors, such as *H. pylori* infection and gastric atrophy, is needed. A large prospective cohort study with a large number of healthy participants as a screening population is required to define major risk factor subgroups and quantify the exact gastric cancer risk in each group. Data of this type will be of great value, particularly in parts of the world where endoscopic screening is impractical.

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