Chapter 3.9.

Gastric cancer prevention in the Republic of Korea

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Summary

- Gastric cancer had been the most commonly occurring cancer type in the Republic of Korea for a long time, but in 2021 it became the fourth most common cancer type, after a steady decrease in incidence since 2011.
- Since 2001, the nationwide gastric cancer screening programme in the Republic of Korea recommends screening with a 2-year interval for adults aged ≥ 40 years using mainly upper endoscopy. The screening programme, with upper endoscopy as the main modality, has been shown to reduce gastric cancer mortality.
- In randomized controlled trials conducted in the Republic of Korea, *H. pylori* treatment in high-risk groups (patients who underwent endoscopic resection for early gastric cancer or family members of patients with gastric cancer) reduced gastric cancer risk by 50%.
- A large-scale clinical trial (HELPER), currently under way in the Republic of Korea in collaboration with IARC, is investigating the efficacy of *H. pylori* eradication as a primary prevention strategy in the general population.

3.9.1 Gastric cancer statistics

In the Republic of Korea, cancer has been the leading cause of death since 1982 [1]. In 1996, the National Plan for Cancer Control was initiated to address this public health problem, and the fourth stage of the plan was initiated in 2021. The Korean Central Cancer Registry reports national cancer statistics annually, with a 2-year lag time. According to the 2021 statistics, published at the end of 2023, the age-standardized rate, standardized to the Korean 2020 standard population, showed that gastric cancer was the most frequently diagnosed cancer until 2018. In 2021, gastric cancer ranked as the

fourth most common cancer type, after thyroid cancer, colorectal cancer, and lung cancer (Fig. 3.9.1) [2]. In 2000–2011, the gastric cancer incidence rate (per 100 000 population) remained stable at > 80; since then, it has gradually decreased, by 4.4% each year, from 84.8 in 2011 to 55.3 (76.3 for men and 38.2 for women) in 2021. Compared with other parts of the world, the age-standardized rate of gastric cancer, adjusted using the Segi world standard population, was 27.5 per 100 000 person-years (38.9 per 100 000 person-years for men and 17.5 per 100 000 person-years for women) in 2021 [1].

The gastric cancer screening rate decreased during the COVID-19 pandemic in 2020, but it surged in 2021, which explains the rebound in gastric cancer incidence in the national cancer statistics [3, 4]. From the cancer incidence data up to 2021, gastric cancer is expected to be ranked the fifth most common cancer type in the Republic of Korea, because of the increasing incidence of breast cancer [5].

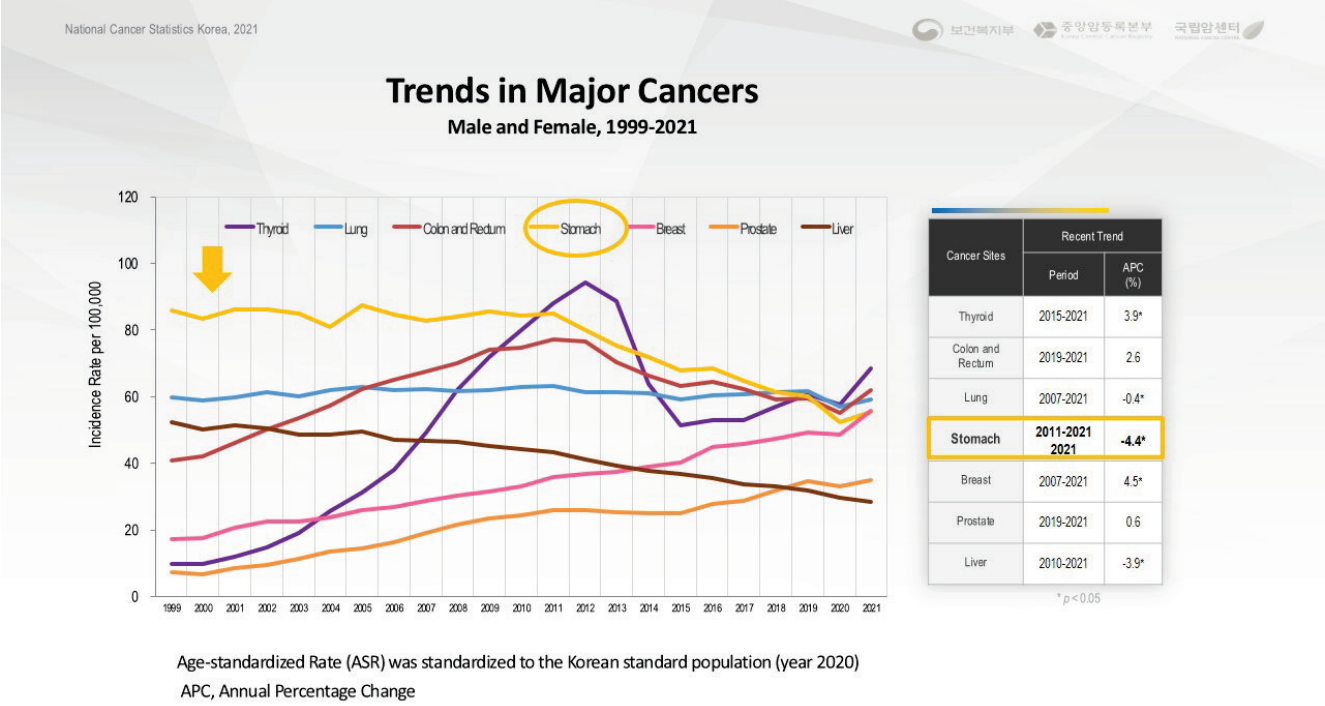

Fig. 3.9.1. Trends in the age-standardized incidence rates of the major cancer types in the Republic of Korea. Gastric cancer incidence rates were stable until about 2011. Since then, the incidence rate has decreased, and gastric cancer became the fourth most common cancer type in 2021. APC, annual percentage change. Compiled from Korean Statistical Information Service (2024) [2].

3.9.2 Gastric cancer stage distributions and mortality rates

The gastric cancer stage distribution in the Republic of Korea in 2019, according to the stage categories of the United States Surveillance, Epidemiology, and End Results (SEER) Program, was 64.3% for localized, 10.9% for regional, and 10.9% for distant stages. The prognosis worsened with increasing stage, with 5-year relative survival rates of 97.0% for localized, 62.1% for regional, and 6.4% for distant stages [6].

In 2021, the crude gastric cancer mortality rate (per 1000 000 population) was 14.1 (18.6 for men and 9.6 for women), and the age-standardized mortality rate was 5.9 (8.9 for men and 3.5 for women) [1]. The 5-year overall survival rate for patients with gastric cancer increased markedly, from 55.7% in 1999–2005 to 77.0% in 2013–2019 [7].

3.9.3 Introduction of the KNCSP for secondary prevention

In 1996, the Government of the Republic of Korea initiated a comprehensive 10-year cancer control plan. In 1999, the Korean National Cancer Screening Program (KNCSP) was launched to provide free-of-charge screening for gastric cancer, breast cancer, and cervical cancer via medical aid beneficiaries. In 2001, formal consensus guidelines for screening were developed for gastric cancer, liver cancer, colorectal cancer, breast cancer, and cervical cancer [8]. For gastric cancer, screening with a 2-year interval for adults aged ≥ 40 years is recommended using upper endoscopy or radiological evaluation (upper gastrointestinal series [UGIS]). The screening modality was chosen based on the participants' preferences and comorbidities [9]. Initially, most participants chose UGIS (74.7% in 2002); the proportion of endoscopy examinations gradually increased, to 70.8% in 2011 [10]. In 2015, the guidelines for gastric cancer screening were revised to place the upper age limit at 74 years and to recommend endoscopy over UGIS [11].

3.9.4 Gastric cancer screening rates

The lifetime screening rates for gastric cancer increased markedly, from 52.0% in 2004 to 76.7% in 2010 and 85.5% in 2018 [12]. The screening rates according to the guideline recommendations were lower than the lifetime screening rates: 39.2% in 2004, 65.1% in 2010, and 72.8% in 2018.

Data from the Korean National Cancer Screening Survey show that the organized screening rate for gastric cancer increased from 38.2% in 2009 to 70.8% in 2022,

whereas the opportunistic screening rate for gastric cancer decreased from 18.8% in 2009 to 4.5% in 2022 [13]. The increasing rate for organized screening can be explained by the very low out-of-pocket cost, because participants need to pay either 0% or 10% of total screening costs, according to their income levels. Therefore, the recent high participation rates for the organized screening programme have almost eliminated socioeconomic inequalities for gastric cancer screening in the Republic of Korea.

3.9.5 Effectiveness of the KNCSP in reducing gastric cancer mortality

The most important parameter for the effectiveness of gastric cancer screening is a reduction in mortality. A nested case–control study was performed using the KNCSP database and including the target population eligible for the screening programmes in 2002 and 2003 [14]. The study involved 54 418 patients with gastric cancer who died in 2004–2012 and living matched controls at a 1:4 ratio. Gastric cancer mortality decreased by 21% (odds ratio [OR], 0.79; 95% confidence interval [CI], 0.77–0.81) in the population who participated in screening compared with people who had never been screened. Gastric cancer mortality decreased by 47% among patients who underwent screening with endoscopy (OR, 0.53; 95% CI, 0.51–0.56). In contrast, no significant reduction in gastric cancer mortality was observed in individuals who underwent screening with UGIS (OR, 0.98; 95% CI, 0.95–1.01). The reduction in gastric cancer mortality increased as the number of endoscopy screenings per individual increased (OR for 1 screening, 0.60; 95% CI, 0.57–0.63; OR for 2 screenings, 0.32; 95% CI, 0.28–0.37; OR for ≥ 3 screenings, 0.19; 95% CI, 0.14–0.26). A significant reduction in gastric cancer mortality via endoscopy screening was observed in all the 5-year age groups in people aged 40–75 years but not in those aged ≥ 75 years [14].

Another cohort study of participants from four geographical areas in the Republic of Korea reported a 42% reduction in gastric cancer mortality among participants who underwent screening with endoscopy (hazard ratio [HR], 0.58; 95% CI, 0.36–0.94) compared with unscreened participants. Screening with UGIS did not significantly reduce gastric cancer mortality (HR, 0.91; 95% CI, 0.36–2.33) [15].

A nationwide population-based study using the Korean National Health Insurance Big Database included all patients with gastric cancer aged ≥ 40 years between 2004 and 2013. Patients with gastric cancer who participated in the gastric cancer screening programme (n = 116 775) showed a significantly better prognosis (41% decreased HR

for gastric cancer death) compared with those who did not participate in screening (non-screening group, $n = 74\,927$). In addition, medical care expenses were significantly lower in the screening group [16].

3.9.6 Gastric cancer stage migration

Stage migration of gastric cancer to earlier stages is a favourable outcome of the KNCSP. In a cohort consisting of 19 168 patients with gastric cancer, those who underwent endoscopy screening were significantly more likely to be diagnosed with a localized SEER cancer stage compared with those who were screened with UGIS (adjusted OR, 1.71; 95% CI, 1.55–1.89) or those who were not screened (adjusted OR, 2.10; 95% CI, 1.90–2.33) [17]. Another cohort study, including 18 414 individuals, evaluated the effects of repeated endoscopy screening on the early detection of gastric cancer [18]. The group of participants who underwent endoscopy screening within 2 years had a significantly higher proportion of early gastric cancer (96% vs 71%; $P = 0.01$) and were more frequently treated with endoscopic resection (54% vs 23%; $P = 0.007$) compared with those who did not undergo endoscopy screening within 2 years. The Korean Gastric Cancer Association reported nationwide survey data showing that the proportion of patients with early gastric cancer who had surgical treatment increased from 28.6% in 1995 to 63.6% in 2019 [19].

Data from the National Cancer Center showed that the proportion of early gastric cancer in surgically treated patients in the Republic of Korea increased from 39% in 2001 to 73% in 2016, whereas the proportion of early gastric cancer in the United States SEER data was almost stable at 23–26% from 2004 to 2016 [20].

3.9.7 Safety of gastric cancer screening and its effect on oesophageal cancer mortality

Endoscopy is a relatively safe procedure, but it sometimes leads to complications, such as bleeding or perforation. In a nationwide survey of about 2.1 million diagnostic endoscopies at 50 hospitals in 2013–2017, the incidence of bleeding was 0.012% and the incidence of perforation was 0.001% [21]. In addition, health insurance claims data in 2017 showed that in diagnostic upper endoscopies in outpatient departments the rate of bleeding was 0.028% and the rate of perforation was 0.003% [21]. The KNCSP for

gastric cancer, which uses endoscopy, is associated with fewer adverse events, and these are tolerated given the benefits of screening.

Oesophageal cancer usually has a poor prognosis, because of its rapid growth and early metastasis. It can be detected during gastric cancer screening using endoscopy or UGIS. A population-based cohort study using the KNCSP database included 16 969 patients diagnosed with oesophageal cancer in 2007–2014 [22]. Oesophageal cancer mortality decreased significantly, by 50%, in participants who were screened with endoscopy (adjusted HR, 0.50; 95% CI, 0.46–0.53). In contrast to findings for gastric cancer, screening with UGIS effectively reduced oesophageal cancer mortality (HR, 0.78, 95% CI, 0.75–0.84) [22].

3.9.8 *H. pylori* infection rates

H. pylori infection is the most important and easily modifiable risk factor for the development of gastric cancer. In 2016–2017, the seroprevalence of *H. pylori* infection in the asymptomatic Korean population aged > 18 years was 43.9% [23]. Over the past two decades, the *H. pylori* infection rate has decreased, from 66.9% in 1998 to 59.6% in 2005 and 54.4% in 2011. From 1998 to 2016–2017, *H. pylori* seroprevalence decreased in all age groups; the decrease was largest in the age group 30–39 years (from 74% to 29%) and smallest in the age group ≥ 70 years (from 67% to 52%) (Fig. 3.9.2) [23]. The proportion of patients with a history of *H. pylori* eradication increased, from 13.9% in 2005 to 19.3% in 2011 and 23.5% in 2017. The decrease in *H. pylori* seroprevalence and the increase in history of *H. pylori* eradication are expected to affect the incidence of gastric cancer in the Republic of Korea [23].

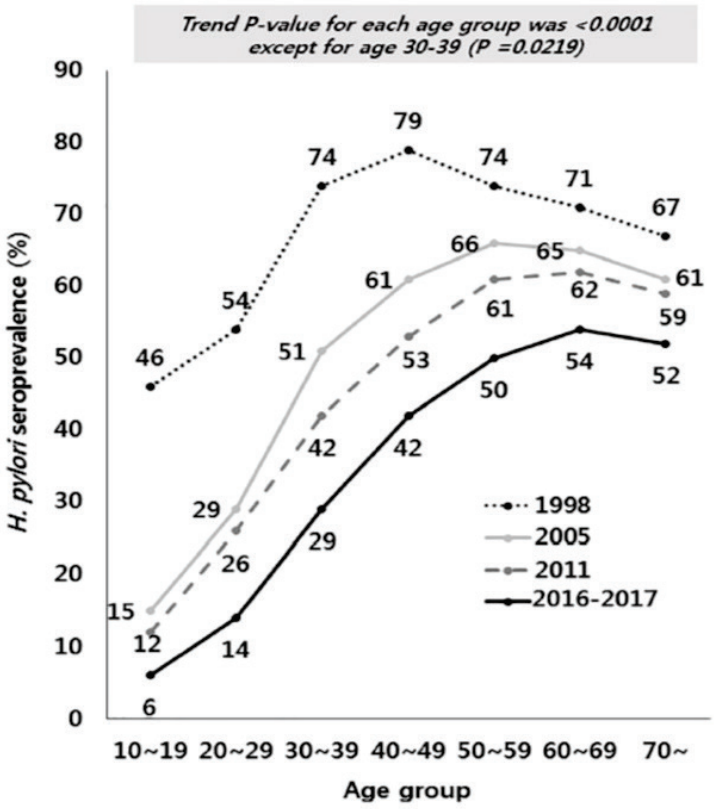

Fig. 3.9.2. Trends in the seroprevalence of *H. pylori* infection in asymptomatic individuals without a history of *H. pylori* eradication therapy, stratified by age group, in 1998, 2005, 2011, and 2016–2017. Adapted from Lim et al. (2018) [23]. © 2018 Lim et al. Article available under the Creative Commons CC BY 4.0.

3.9.9 *H. pylori* treatment trial for prevention of metachronous gastric cancer

The primary prevention strategy of eradicating *H. pylori* infection has not been incorporated into the KNCSP. However, the *Helicobacter pylori* Eradication for Gastric Cancer Prevention in the General Population (HELPER) trial, a large-scale clinical trial (see Section 3.9.11), is currently investigating this strategy in the general population in the Republic of Korea. This is because a primary prevention trial should be performed in a large-scale, long-term follow-up study. A study in a high-risk group can make a clinical trial feasible by reducing the size of the study population needed, reducing the follow-up duration required, and improving the compliance of the study participants.

The first such study was performed in a group at very high risk who underwent endoscopic resection for early gastric cancer, to show that eradicating *H. pylori* infection

could reduce the risk of the development of new gastric cancer (i.e. metachronous gastric cancer) [24]. A total of 396 patients were included in the study from 2003 to 2013. During the 13 years (median, 5.9 years) of follow-up, metachronous gastric cancer developed in 7.2% (14 of 194) of participants in the treatment group and in 13.4% (27 of 202) of participants in the placebo group (HR in the treatment group, 0.5; $P = 0.03$) (Fig. 3.9.3A) [24]. In the analysis according to the *H. pylori* eradication status after treatment, metachronous gastric cancer developed in 14.0% (32 of 228) of the patients with persistent *H. pylori* infection and in 5.4% (9 of 167) of the patients in whom *H. pylori* infection had been eradicated (HR in patients with eradicated infection, 0.32; $P = 0.002$).

The study also showed that improvement in the grade of atrophy in the gastric body was more frequent in the treatment group than in the placebo group (48.4% vs 15.0%; $P < 0.001$). In addition, improvement in the grade of intestinal metaplasia in the gastric body was more frequent in the treatment group than in the placebo group (36.6% vs 18.3%; $P < 0.001$) [24].

3.9.10 *H. pylori* treatment trial in first-degree family members of patients with gastric cancer

The second study in a high-risk group included first-degree relatives of patients with gastric cancer, who had an almost 3-fold increased risk of gastric cancer (OR, 2.92; 95% CI, 2.402–3.552) [26]. A total of 1838 participants with *H. pylori* infection were enrolled in this study in 2004–2011 [25]. During the 14 years (median, 9.2 years) of follow-up, gastric cancer developed in 1.2% (10 of 832) of participants in the treatment group and in 2.7% (23 of 844) of participants in the placebo group (HR in the treatment group, 0.45; $P = 0.03$) (Fig. 3.9.3B). In the analysis according to the *H. pylori* eradication status after treatment, gastric cancer developed in 2.9% (28 of 979) of the patients with persistent *H. pylori* infection and in 0.8% (5 of 608) of the patients in whom *H. pylori* infection had been eradicated (HR in patients with eradication of infection, 0.27; 95% CI, 0.10–0.70) [25].

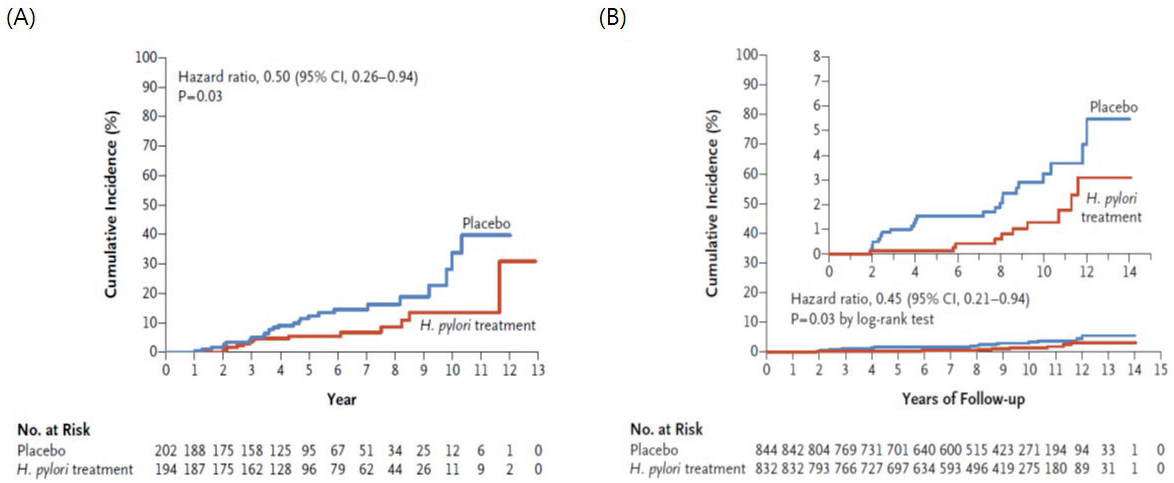

Fig. 3.9.3. Cumulative incidence of gastric cancer after treatment for *H. pylori* infection. (A) Kaplan–Meier curves for the cumulative incidence of metachronous gastric cancer starting 1 year after endoscopic resection of gastric cancer. During a median follow-up of 5.9 years, metachronous gastric cancer developed in 7.2% (14 of 194) of participants in the treatment group and in 13.4% (27 of 202) of participants in the placebo group. (B) Kaplan–Meier curves for the primary outcome of development of gastric cancer. During a median follow-up of 9.2 years, gastric cancer developed in 1.2% (10 of 832) of participants in the treatment group and in 2.7% (23 of 844) participants in the placebo group. The inset shows the same data on an enlarged *y* axis. (A) Reprinted from Choi et al. (2018) [24]. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. (B) Reprinted from Choi et al. (2020) [25]. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

H. pylori treatment with triple therapy of a proton pump inhibitor, clarithromycin, and amoxicillin, which has shown an eradication rate of about 70%, could reduce the risk of gastric cancer by 55% in family members of patients with gastric cancer in the absence of further rescue therapy. In the secondary outcome analysis, patients with confirmed eradication of *H. pylori* infection had a 73% lower risk of gastric cancer compared with those with persistent *H. pylori* infection [25]. Therefore, tests for successful *H. pylori* eradication should be performed to increase the effectiveness of gastric cancer prevention.

3.9.11 HELPER trial in the general population

In collaboration with IARC, a large population-based trial (the HELPER study) was initiated in 2014 to evaluate whether *H. pylori* treatment can reduce the risk of gastric

cancer in the asymptomatic general population in the Republic of Korea (ClinicalTrials.gov ID, NCT02112214). The study had screened *H. pylori* infection status in > 12 000 Korean individuals at average risk who had participated in the KNCSP until 2019. Individuals with *H. pylori* infection were randomized to receive either bismuth quadruple therapy for *H. pylori* eradication or placebo. The participants will undergo biennial endoscopy through the KNCSP for 10 years, and an interim analysis is planned after a 6-year follow-up period if two thirds of the expected target number of gastric cancers have developed by that time point. As of December 2024, about 35 cases of gastric cancer (> 60% of the target number) had been reported. The primary outcome of the trial is the incidence of gastric cancer in the treatment and placebo groups. The study will provide high-quality evidence on the *H. pylori* eradication strategy for gastric cancer prevention in the average-risk population in the Republic of Korea; the KNCSP will be modified according to the results of the trial.

3.9.12 Criteria for *H. pylori* treatment in the KNHIS

In 2024, *H. pylori* treatment was permitted by the Korean National Health Insurance Service (KNHIS) for patients with the following indications: (i) peptic ulcer disease (benign gastric ulcer and duodenal ulcer), (ii) low-grade mucosa-associated lymphoid tissue (MALT) lymphoma, (iii) post-treatment (endoscopic resection or surgical resection) status of early gastric cancer, (iv) idiopathic thrombocytopenic purpura, and (v) post-endoscopic resection status of gastric adenoma. *H. pylori* treatment for patients with post-treatment status has been included since 2018 based on the results of a randomized controlled trial of patients with early gastric cancer who underwent endoscopic resection [24]. The KNHIS does not yet cover *H. pylori* treatment for first-degree relatives of patients with gastric cancer or for healthy asymptomatic individuals with atrophic gastritis; however, *H. pylori* treatment can be prescribed if patients pay all the costs for the treatment. The indications for *H. pylori* treatment covered by the KNHIS are expected to expand based on the results of the HELPER study.

3.9.13 Trial of low-dose aspirin for prevention of metachronous gastric cancer

Aspirin is a promising chemopreventive drug for gastrointestinal tract cancers, particularly colorectal cancer. A meta-analysis reported that long-term aspirin use was associated with a reduced risk of gastrointestinal cancers, including gastric cancer [27]. The National Cancer Center started a randomized clinical trial to show that daily use of

low-dose (100 mg) aspirin for 5 years can reduce the risk of new gastric cancer in patients with early gastric cancer after endoscopic resection (ClinicalTrials.gov ID, NCT04214990). About 1700 participants will be recruited by 2025, and participants will be followed up until 2030.

3.9.14 Assessment of gastric cancer risk by evaluation of atrophy

Atrophic gastritis is the main risk factor for the development of gastric cancer. An objective and accurate assessment of the severity of gastric atrophy is essential for proper risk stratification. The most common methods include endoscopic evaluation, serological tests for pepsinogen I and II levels, and histological assessment.

Endoscopic assessment using the Kimura–Takemoto classification is a non-invasive method for evaluating gastric atrophy [28]. Interobserver variation for this assessment is high, especially among inexperienced endoscopists, and agreement rates can improve after training [29].

The pepsinogen test is a serological test. A serum pepsinogen I level of < 70 mg/mL and a serum pepsinogen I/II ratio of < 3 are accepted criteria for severe gastric glandular atrophy. This method is objective and non-invasive, but the absence of reference value standardization among commercially available test kits is a major limitation. Test results are usually affected by *H. pylori* status, age, sex, smoking, alcohol consumption, dietary habits, hormone levels, and use of medication [30, 31].

The updated Sydney system suggests using a visual analogue scale for biopsy specimens obtained from the antrum including the gastric angle and from the corpus for the histological assessment of atrophy or intestinal metaplasia [32]. Although histological assessment can be considered the reference standard for evaluation of gastric atrophy, interobserver agreement was low among gastrointestinal pathologists in the Republic of Korea, especially for atrophy (kappa value, 0.19 for atrophy; 0.52 for intestinal metaplasia) [33]. Interobserver variability can be reduced by consensus among pathologists and education.

The Operative Link on Gastritis Assessment (OLGA) and the Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) have been suggested to estimate the risk of gastric cancer development using histological data from the updated Sydney system [34, 35]. In Korean patients with gastric cancer, high-risk stages (OLGA or

OLGIM stages III and IV) were associated with risk of intestinal-type gastric cancer but not with risk of diffuse-type gastric cancer [36]. In the general population in the Republic of Korea, the proportion of high-risk OLGA stages was 6.9% for ages < 40 years but increased gradually, to 23.0% for ages 40–49 years, 29.1% for ages 50–59 years, and 41.1% for ages 60–69 years [37]. A study in Italy with 1755 participants showed that OLGA stages III and IV could reliably predict gastric cancer development [38]. Therefore, a long-term prospective study in the Republic of Korea is urgently needed to evaluate the usefulness of the OLGA and OLGIM systems. The most accurate and cost-effective of the three methods for assessment of atrophy (endoscopic, serological, and histological) should be determined to effectively select high-risk groups from the general population in the Republic of Korea.

3.9.15 Future directions

H. pylori infection and gastric atrophy are two major factors to consider in the risk stratification of gastric cancer. In the Republic of Korea, most patients with gastric cancer have current or past *H. pylori* infection. However, the prevalence of *H. pylori* infection in the younger age group has continuously decreased. The current KNCSP for gastric cancer recommends endoscopy screening with a 2-year interval without risk stratification for adults aged ≥ 40 years. This policy may result in overutilization of medical resources, a high socioeconomic burden, or problems associated with overdiagnosis.

The following areas of research are urgently needed to modify the KNCSP by introducing the primary prevention strategy of *H. pylori* eradication into the current secondary prevention strategy. First, the effect of *H. pylori* eradication on gastric cancer incidence and mortality rates should be properly evaluated in high-quality clinical trials involving the general population. Second, proper estimation of the association of atrophy or intestinal metaplasia with risk of gastric cancer after *H. pylori* eradication should be performed. Third, the differential effects of *H. pylori* infection and gastric atrophy according to the histological type of gastric cancer should be determined, because intestinal-type and diffuse-type gastric cancers have different clinicopathological characteristics. Fourth, early-onset gastric cancer (i.e. at ages < 40 years) was also associated with *H. pylori* infection. The most appropriate age for screening and treatment of *H. pylori* infection needs to be determined.

In the Republic of Korea, the effects of endoscopy in gastric cancer screening programmes to reduce gastric cancer mortality have been well established. Further improvement of this secondary screening strategy by introducing surveillance based on gastric cancer risk factors, such as *H. pylori* infection and gastric atrophy, is required. The ongoing large prospective trial in the National Cancer Center, in collaboration with the HELPER trial and a prospective cohort study with well-defined endoscopic, histological, and serological data, will provide answers to many of these critical questions.

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