

Diagnosis and Management of High Risk Group for Gastric Cancer

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Gastric cancer is associated with high morbidity and mortality worldwide. To reduce the socioeconomic burden related to gastric cancer, it is very important to identify and manage high risk group for gastric cancer. In this review, we describe the general risk factors for gastric cancer and define high risk group for gastric cancer. We discuss strategies for the effective management of patients for the prevention and early detection of gastric cancer. Atrophic gastritis (AG) and intestinal metaplasia (IM) are the most significant risk factors for gastric cancer. Therefore, the accurate selection of individuals with AG and IM may be a key strategy for the prevention and/or early detection of gastric cancer. Although endoscopic evaluation using enhanced technologies such as narrow band imaging-magnification, the serum pepsinogen test, *Helicobacter pylori* serology, and trefoil factor 3 have been evaluated, a gold standard method to accurately select individuals with AG and IM has not emerged. In terms of managing patients at high risk of gastric cancer, it remains uncertain whether *H. pylori* eradication reverses and/or prevents the progression of AG and IM. Although endoscopic surveillance in high risk patients is expected to be beneficial, further prospective studies in large populations are needed to determine the optimal surveillance interval. (**Gut Liver 2015;9:5-17**)

Key Words: Stomach neoplasms; Risk factors; Risk management

INTRODUCTION

Gastric cancer remains the second leading cause of cancer death worldwide.¹ Because gastric carcinogenesis is a multistep and multifactorial process,² identification of risk factors participating in each carcinogenic step and appropriate manage-

ment of these risk factors could reduce the incidence of gastric cancer. For example, the identification of *Helicobacter pylori* as a causal factor of gastric cancer and targeted eradication have reduced the incidence of gastric cancer worldwide over the last 50 years. However, other factors that include recently increasing unhealthy diet and obesity could also be influential in the incidence of gastric cancer.

Further reduced mortality of gastric cancer demands the identification of high risk group for gastric cancer and development of management strategies to slow/prevent progression of gastric cancer. In addition, it is more cost-effective to detect gastric cancer in an early stage, since it is more readily treated by endoscopic submucosal resection (ESD) than is more advanced gastric cancer.

The aim of this review is to discuss effective management strategies in high risk group for gastric cancer, especially focusing on Asian countries where gastric cancer incidence is still high. We review general risk factors of gastric cancer, define high risk group for gastric cancer, and discuss how to effectively manage them to prevent the development of gastric cancer and detect gastric cancer in an early stage.

RISK FACTORS OF GASTRIC CANCER

Meta-analyses investigating the risk of gastric cancer with each risk factor are summarized in Table 1. The following are separate discussions about each risk factor of gastric cancer.

1. *H. pylori*

The causal association between *H. pylori* infection and gastric cancer is firmly established by many epidemiologic and clinical studies. Gastric cancer develops in approximately 1% of *H. pylori*-infected subjects.³ Inversely, more than 90% of gastric cancer patients have current or past *H. pylori* infection.^{4,5} In a

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Table 1. Summary of Meta-Analyses Investigating the Risk of Gastric Cancer with Each Risk Factor

Risk factor	Author (year)	No. of studies	No. of subjects	Risk estimates* (95% CI)	p-value
<i>H. pylori</i> infection	Huang <i>et al.</i> (1998) ⁶	19	6,450	1.92 (1.32–2.78)	NA
	Xue <i>et al.</i> (2001) ⁷	11	12,467	3.00 (2.42–3.72)	<0.001
Salt intake	D'Elia <i>et al.</i> (2012) ¹⁰	7	268,718	1.68 (1.17–2.41) [†]	0.005
Smoking	Ladeiras-Lopes <i>et al.</i> (2008) ¹²	23	NA	1.53 (1.42–1.65) [‡]	NA
	La Torre <i>et al.</i> (2009) ¹³	22	61,723	1.69 (1.35–2.11) [‡]	<0.001
Alcohol	Tramacere <i>et al.</i> (2012) ¹⁴	13	NA	1.20 (1.01–1.44) [§]	0.001
Fiber intake	Zhang <i>et al.</i> (2013) ²²	21	580,064	0.58 (0.49–0.67)	<0.001
Family history of gastric cancer	Rokkas <i>et al.</i> (2010) ²⁷	8	2,355	1.98 (1.76–2.88)	<0.001
Obesity	Chen <i>et al.</i> (2013) ²⁸	13	9,017,901	1.06 (0.99–1.12) [¶]	0.490

CI, confidence interval; *H. pylori*, *Helicobacter pylori*; NA, not available.

*Risk estimates are expressed as relative risk or odds ratio according to the type of included studies (cohort or case-control); [†]High salt intake group compared with low salt intake group; [‡]Current smokers compared with never smokers; [§]Heavy alcohol drinkers (≥ 4 drinks per day) compared with nondrinkers; ^{||}The highest fiber intake group compared with the lowest fiber intake group; [¶]Obese (BMI, ≥ 30 kg/m²) compared with normal (BMI, 18.5 to 24.9 kg/m²).

meta-analysis of 19 cohort or case-control studies including 2,491 patients and 3,959 controls, the odds ratio (OR) for gastric cancer in patients with *H. pylori* infection by serology has been reported as 1.92 (95% confidence interval [CI], 1.32 to 2.78).⁶ Succeeding meta-analysis of 11 case-control studies including larger subjects also reported strong association between *H. pylori* infection and gastric cancer (OR for gastric cancer in *H. pylori*-infected subject, 3.00; 95% CI, 2.42 to 3.72).⁷ *H. pylori* is the main risk factor of gastric cancer.

2. Salt and salt-preserved foods

Although several mechanisms by which salt intake may increase risk of gastric cancer have been postulated, to date there has been no consistent conclusion.⁸ However, the weight of ecological, case-control and cohort studies strongly support the relationship between high intake of salt, salt-preserved foods and increased risk of gastric cancer.⁹ A recent meta-analysis showed that dietary salt intake was directly associated with risk of gastric cancer in prospective population studies, with progressively increasing risk across consumption levels.¹⁰ However, the absolute increase of risk of gastric cancer was not high, even in high salt intake group (compared with low salt intake group, relative risk [RR], 1.68; 95% CI, 1.17 to 2.41).¹⁰ In addition, a meta-analysis reported that an association between salt intake and intestinal metaplasia (IM) is not significant.¹¹ Therefore, surveillance for gastric cancer in a high salt intake population might not be needed. Moreover, there is no study regarding practical strategy for prevention of gastric cancer in relation to salt and salted food consumption.

3. Smoking

Meta-analysis including 23 articles concluded that the summary RR estimates for gastric cancer in current smokers was

1.53 compared with never smokers.¹² Succeeding meta-analysis including 14,442 cases and 73,918 controls showed similar results (comparing never smokers, OR for gastric cancer in current smoker, 1.69; 95% CI, 1.35 to 2.11).¹³ However, mechanisms by which smoking increase risk of gastric cancer are not well known.

4. Alcohol

Whether alcohol drinking increases the risk of gastric cancer is unclear. A recent meta-analysis involving 44 case-control and 15 cohort studies including a total of 34,557 gastric cancer cases reported a positive association between the risk of gastric cancer and only heavy alcohol drinking (four or more drinks per day).¹⁴ Compared with nondrinkers, the pooled RR was 1.20 (95% CI, 1.01 to 1.44) for heavy alcohol drinkers. In contrast, although the number of included studies was small, a recent meta-analysis reported that drinking cessation has no significant effect on risk of gastric cancer.¹⁵ However, the effect of alcohol drinking on risk of gastric cancer might vary with the cancer's location (cardiac cancer vs noncardiac cancer)¹⁴ and a study suggested that aldehyde dehydrogenase 2 (*ALDH2*) polymorphisms were found to modify the susceptibility to the development of gastric cancer associated with alcohol intake.¹⁶ For *ALDH2*, neither dominant nor allele model is relevant. *ALDH2* genetic polymorphism appears to modify the susceptibility to upper aero-digestive tract cancers induced by alcohol intake. Therefore, it is necessary to consider alcohol consumption as well as *ALDH2* genetic polymorphism. That is, the *ALDH2* *2 allele is translated into an inactive protein subunit, leading to an inability to metabolize acetaldehyde and causes the accumulation of acetaldehyde after the ingestion of alcohol. Peak blood acetaldehyde concentrations after an alcohol challenge were reportedly 18 and 5 times higher, among homozygous *ALDH2*

*2 variants and heterozygous variants, respectively, compared to homozygous wild type individuals.¹⁷ As acetaldehyde is a plausible candidate for the carcinogenic effect of alcoholic drinks, *ALDH2* genetic polymorphism may play a pivotal role on alcohol-induced carcinogenesis. Another point is that there are significant differences in alcohol consumption according to the *ALDH2* genotype (Mendelian randomization). That is, *ALDH2* *1/*2 heterozygotes had a lower level of alcohol consumption than *1/*1 homozygotes (wild-type), and most of the *ALDH2* *2/*2 carriers were never/rare drinkers. *ALDH2* genotype can be used as a proxy for alcohol intake.¹⁸ For instance in esophageal carcinogenesis, *ALDH2* *2/*2 genotype reduces esophageal cancer risk due to a lower alcohol intake; *ALDH2* *1/*2 is associated with a 3-fold overall increase in risk for esophageal cancer. The association between *ALDH2* *1/*2 genotype and esophageal cancer is dependent on alcohol consumption. Among nondrinkers, there is no evidence of an increased risk for esophageal cancer; among heavy drinkers, a significantly increased risk is observed. Existence of an *ALDH2* *2 allele *per se* does not increase risk of esophageal cancer unless alcohol is consumed. In case of gastric cancer subjects with inactive *ALDH2* *2 allele(s) showed a lower level of alcohol consumption than *ALDH2* *1/*1 homozygotes ($p < 0.001$). Among the *ALDH2* *1/*2 carriers ($n=243$), current/ex-drinkers had a significantly increased risk for gastric cancer compared to never/rare drinkers (OR, 2.80; 95% CI, 1.51 to 5.19). Among heavy drinkers ($n=115$), *ALDH2* *1/*2 heterozygotes had a 4-fold increased risk for gastric cancer compared to *1/*1 homozygotes (OR, 4.26; 95% CI, 1.10 to 16.47); however, no risk increase was seen among never/rare drinkers.¹⁶

5. Dietary fiber intake

A possible role of dietary fiber in preventing gastric cancer has not been as strongly established as in colorectal cancer. The importance of nitrous compounds in the stepwise carcinogenesis of gastric cancer has been suggested.^{19,20} The effect of dietary fiber as nitrite scavengers was reported in an experimental study; wheat bran reduced the nitrite concentration and the capability of nitrite scavenging was stronger in lower pH.²¹ Although several clinical studies conducted since the 1980s have addressed whether dietary fiber intake could decrease the risk of gastric cancer, the results have been conflicting. A recent meta-analysis of 21 studies involving 580,064 subjects showed that ORs of gastric cancer for the highest, compared with the lowest, dietary fiber intake was 0.58 (95% CI, 0.49 to 0.67). In addition, there was a dose-response association; a 10-g/day increment in fiber intake was linked with a significant (44%) reduction in gastric cancer risk.²² However, the absolute magnitude was less certain because of heterogeneity among the studies ($p < 0.001$, $I^2=62.2\%$).

6. Low socioeconomic status

Several studies have suggested that gastric cancer develops

more frequently in lower socioeconomic groups.^{23,24} However, these studies are dated and there has been no recent meta-analysis or well-organized systematic review mainly focused on the association between socioeconomic status and risk of gastric cancer. A recent Korean study analyzing the risk of gastric cancer in relatives of patients with gastric cancer indicated that lower socioeconomic status increased the risk of gastric cancer in a multivariate analysis (current income less than US \$1,000/month compared with income over US \$5,000; OR, 2.16; 95% CI, 1.25 to 3.71; $p=0.006$).²⁵ However, as lower socioeconomic status includes various confounding factors like diet, living standards, and sanitation, further studies are required.

7. Family history of gastric cancer

Members of the same family tend to have similar environmental factors like socioeconomic status and dietary habit, and there is a possibility that the same strain of *H. pylori* infection is also clustered. Therefore, the results of studies conducted to elucidate whether family history of gastric cancer is/is not an independent risk factor of gastric cancer should be interpreted very cautiously. A population-based, statewide, case-control study from Germany reported that *H. pylori* infection and a family history were strong independent risk factors for gastric cancer, although both were positively related with one another.²⁶ A Korean study also showed that adjusted OR for gastric cancer increased 3-fold for subjects with first-degree relatives with gastric cancer (OR, 2.85 in comparison with control; 95% CI, 1.83 to 4.46).²⁵ In addition, a recent meta-analysis reported that family history of gastric cancer increases the risk of *H. pylori* infection, atrophic gastritis (AG), and IM by approximately 2-fold each.²⁷

8. Obesity

Unlike colonic and esophageal adenocarcinomas in which obesity is a major risk factor, studies on the association between obesity and gastric cancer have shown conflicting results. A recent meta-analysis including 24 prospective studies found that overweight (body mass index [BMI], 25 to 30 kg/m²) and obesity (BMI, ≥ 30 kg/m²) were associated with an increased risk of gastric cardiac cancer (RR, 1.21, 95% CI, 1.03 to 1.42 for overweight and RR, 1.82, 95% CI, 1.32 to 2.49 for obesity) but not with noncardiac cancer (RR, 0.93, 95% CI, 0.82 to 1.05 for overweight and RR, 1.00, 95% CI, 0.87 to 1.15 for obesity).²⁸ However, no study has adjusted for *H. pylori* infection status, which could be a major weakness. In addition, another confounding factor is staging differences related to BMI. Further well-designed studies are needed considering *H. pylori* infection status and other confounding factors.

9. Precancerous lesions for gastric cancer

1) Atrophic gastritis

A well-known hypothesis posits that gastric cancer develops through a cascade of precursor lesions (chronic superficial

gastritis, AG, IM, and dysplasia) after *H. pylori* infection.² A nationwide cohort study in The Netherlands showed that risk of gastric cancer increased in a step-wise manner according to the severity of premalignant gastric lesions (annual incidence of gastric cancer within 5 years after diagnosis: 0.1%, 0.25%, 0.6%, and 6% for AG, IM, mild-to-moderate dysplasia, and severe dysplasia, respectively).²⁹ Although the risk of gastric cancer in individuals with AG varies according to the severity of AG, the adjusted RR of gastric cancer in the patients diagnosed as having severe fundal AG was reportedly high (5.76) compared with patients having little or no fundal AG.³⁰

2) Intestinal metaplasia

In the aforementioned The Netherlands study, the annual incidence of gastric cancer within 5 years after diagnosis as IM was 0.25%. In addition, an epidemiological study suggested that patients with IM have more than a 10-fold increased risk of developing gastric cancer.³¹ In a study conducted in a rural Chinese population at high risk of gastric cancer, when residents with precancerous lesions were followed up for 5 years, ORs of gastric cancer in subjects with IM were 17.1 to 29.3.³²

The risk of gastric cancer also depends on the extension and phenotype of IM. Complete metaplasia is diagnosed when the epithelium of gastric mucosa resembles the small intestinal phenotype. By contrast, incomplete metaplasia resembles a colonic epithelium phenotype. IM could be classified as type I, II, and III according to the phenotype of mucin. IM type I (complete) expresses only sialomucins and type III (incomplete) expresses sulfomucins. Type II (incomplete) is a hybrid form expressing a mixture of gastric and intestinal mucins.³³ Several studies reported that the risk of gastric cancer is highest in type III or incomplete IM.^{34,35} However, a contrary study has been published.³⁶ Furthermore, IM subtyping was not found to play a major role in the prediction of gastric cancer development in Korea.³⁷ Therefore, subtyping of IM is not recommended for clinical practice at the present time.³⁸ However, a recent systematic review concluded that most cross-sectional studies reported that the prevalence of incomplete IM was significantly higher in gastric cancer than in other gastric lesions. Moreover, it reported that more than half of the follow-up studies found a statistically significant association between incomplete IM and subsequent gastric cancer risk (RR of gastric cancer, 4- to 11-fold higher for the presence of incomplete type in comparison to complete type or absence of incomplete type). The authors concluded that most of the scientific evidence supports the utility of subtyping IM as a predictor of gastric cancer risk.³⁹

IM tends to appear first at the incisura angularis and extends to the neighboring mucosa in both the antrum and corpus. One study regarding topographic patterns of IM showed that the extension of IM is significantly associated with increased cancer risk.⁴⁰ In addition, it has been proposed that the distribution of IM, rather than the IM subtype, may be of higher predictive

value of gastric cancer risk.³¹

Another subjects deserving mention regarding IM are *CDX1* and *CDX2*, which are member of the caudal-related homeobox gene family and intestinal-specific transcriptional factor.⁴¹ These two genes play an important role in the development of small and large intestine. While normal gastric mucosa does not express *CDX1* and *CDX2*, aberrant expression of *CDX1* and *CDX2* is observed in animal and human gastric IM.⁴² There has been a great diversity of opinion concerning the role of *CDX1* and *CDX2* in gastric carcinogenesis. However, a recent Korean study suggested that aberrant expression of *CDX1* and *CDX2* on transcriptional level correlated with IM grade in the gastric body.⁴³ A subsequent study demonstrated this association between aberrant *CDX2* expression and IM grade of the gastric body at the translational level.⁴⁴ These results suggest that *CDX2* expression might play an important role in the progression of IM and further studies are required to clarify the exact role of *CDX2* in gastric carcinogenesis.

DEFINING HIGH RISK GROUP FOR GASTRIC CANCER

The many identified risk factors differ in their ORs for gastric cancer. Compared with other risk factors, AG and IM increase the risk of gastric cancer exponentially. Therefore, we could define individuals with AG and IM as high risk group for gastric cancer. Key points in the management of those at high risk of gastric cancer could be how to select a risk group among subjects with AG and IM. Several methods to select high risk group for gastric cancer are summarized in Table 2.

1. Endoscopic evaluation

The gold standard for diagnosing AG and IM is a histological study of gastric mucosa. However, the invasive nature of this method precludes its use for population screening. Moreover, biopsy cannot be performed during every gastroscopy. Thus, in many cases endoscopists diagnose AG and IM purely by endoscopy. However, there is a high rate of interobserver variability in the identification of AG and IM by endoscopy. In addition, the endoscopic findings correlate poorly with the histological findings. The diagnostic accuracy of AG and IM by conventional white light endoscopy is not satisfactory. For example, in a large Korean cohort of 1,330 subjects, the sensitivity/specificity of endoscopy for the diagnosis of AG based on histological diagnosis was 61.5%/57.7% in the antrum and 46.8%/76.4% in the body of the stomach.⁴⁵ In the same cohort, the sensitivity/specificity of endoscopic IM diagnosis was 24.0%/91.9% in the antrum and 24.2%/88.0% in the body.⁴⁶

Recently, to increase the accuracy of endoscopic diagnosis of IM, enhanced endoscopic techniques such as magnification and narrow band imaging (NBI) have been studied.⁴⁷ Because combining the NBI system and magnifying endoscopy (ME) allows simple and clear visualization of microscopic structures

Table 2. Methods for the Selection of Patients at High Risk for Gastric Cancer

Method	Strengths	Weaknesses
OLGA	More useful for prediction of gastric cancer than Sydney classification	Low interobserver agreement Invasive and requiring multiple biopsies in the stomach Not suitable for mass screening
OLGIM	Excellent interobserver agreement	Invasive and requiring multiple biopsies in the stomach Not suitable for mass screening
Serum PG test	Noninvasive Well-studied over decades Relatively high negative predictive values High acceptability of population	No uniform method of measurement is available Optimal cutoff values could be affected by several factors
<i>H. pylori</i> serology	Noninvasive Useful for additional selection for high risk group in subjects with low PG level	Cannot be used as single method
Serum TFF 3	Noninvasive Higher positive/negative predictive value for gastric cancer screening than serum PG test Not affected by <i>H. pylori</i> status and aging	Limitation in predicting diffuse-type gastric cancer Data is confined to Japan

OLGA, operative link for gastritis assessment; OLGIM, operative link for gastric intestinal metaplasia; PG, pepsinogen; TFF3, trefoil factor 3; *H. pylori*, *Helicobacter pylori*.

of the superficial mucosa and its capillary patterns, it could be a promising approach for the precise detection of IM without biopsy. Uedo *et al.*⁴⁸ reported that observation of a light blue crest, defined as a fine, blue-white line on the crests of the epithelial surface using the NBI with ME, is a highly accurate sign of the presence of histological IM. The sensitivity and specificity of light blue crest for predicting IM were 89% and 93%, respectively. A recent study used NBI for targeted biopsy and surveillance of gastric IM, and reported that the sensitivity and specificity of first/second surveillance was 78.8%/91.3% and 82.5%/89.1%, respectively.⁴⁹ Similarly, another study reported that NBI increases the diagnostic yield for the detection of IM and dysplasia, and showed that the sensitivity and specificity of NBI were 71% and 58%, respectively.⁵⁰ However, examining the whole stomach by NBI and ME may be difficult and time-consuming. Thus, precise and close examination by white light endoscopy should be initially performed; NBI and ME could be used for further evaluation of specific lesion identified by white light endoscopy.

2. Pathologic evaluation

A recent European guideline suggested that systems for histopathological staging like operative link for gastritis assessment (OLGA) and operative link for gastric IM (OLGIM) assessment may be useful for risk categorization of progression to gastric cancer.³⁸ Focusing on the fact that the Sydney gastritis classification provides little prognostic and therapeutic information for management of patients, in 2007 an international group of

pathologists proposed new gastritis histology reporting to predict gastric cancer risk.⁵¹ The OLGA staging system integrates atrophy score (from 0 to 3 using the Sydney scoring system) and atrophy topography (antrum vs corpus). Patients are classified as stage I to stage IV according to the degree of risk for gastric cancer. Thereafter, a study involving 93 Italian patients followed-up for more than 12 years demonstrated the prowess of the OLGA staging system in predicting the risk of gastric cancer.⁵² However, like the Sydney system, this system also requires five biopsies in the stomach for risk assessment (the greater and lesser curvatures of the distal antrum, the lesser curvature at the incisura angularis, and the anterior and posterior walls of the proximal corpus). Therefore, this system remains limited for use as a population-based screening method.

IM is associated with relatively high interobserver agreement compared with AG. Therefore, replacement of AG by IM in the assessment of gastric cancer risk (OLGIM systems) was proposed in 2010.⁵³ Thereafter, a Dutch study that evaluated premalignant lesions using the OLGIM staging system and followed-up the patients failed to demonstrate OLGIM stage III or IV as risk factors for progression of premalignant lesion, although the authors reported excellent interobserver agreement for IM.⁵⁴ A recent Korean study retrospectively matched 474 gastric cancer patients with health screening control persons and applied the OLGA and OLGIM staging systems. High OLGA and OLGIM stages were independent risk factors for gastric cancer (especially the intestinal type), prompting the suggestion that these two systems could be useful for risk assessment for gastric cancer.⁵⁵

3. Serum pepsinogen test

Since AG can have a patchy distribution, sampling errors in the diagnosis of AG by endoscopic biopsy can be problematic.⁵⁶ In addition, as endoscopy is an invasive examination, it has limitations for use as a mass screening method. For these reasons, pepsinogen (PG) has long been studied as the basis for a serologic test of the assessment of the degree of AG, especially in Japan.

Two biochemically distinct PGs are produced by gastric mucosa. PG I is exclusively produced by chief and mucous neck cells in the fundic glands, while PG II is secreted by these cells and also by the cells in the pyloric glands and Brunner's glands. On the progression of gastritis, initially both PG I and PG II increase. However, because chief cells are replaced by pyloric glands as inflammation becomes aggravated, the level of PG II further increases and the PG I level starts to decrease. As a result, the PG I/II ratio also decreases. Because low serum PG I level and PG I/II ratio reflect gastric atrophy, these markers have been studied as a biomarker to select high risk group for gastric cancer.^{9,57}

In a Japanese study that measured serum PG levels and conducted screening endoscopy in 5,113 subjects, with PG I concentration <70 ng/mL and PG I/II ratio <3 as the cutoff points, the sensitivity and specificity for gastric cancer was 84.6% and 73.5%, respectively.⁵⁸ Based on this study, PG I <70 ng/mL and PG I/II ratio <3 has become widely used as the cutoff value for gastric cancer diagnosis in Japan. For example, in another Japanese study that assessed serum PG and *H. pylori* antibody levels in 5,209 asymptomatic, middle-aged subjects with a subsequent 10-year follow-up, this cutoff value displayed 58.7% sensitivity, 73.4% specificity, and 2.6% positive predictive value for gastric cancer.⁵⁹ In a meta-analysis for the validity of the PG test as a gastric cancer screening method, negative predictive values was reported over 99%, regardless of different cutoff values of PG I and PG I/II ratio.⁶⁰ In addition, gastric cancer screening using the serum PG test method was very high acceptable.⁶¹

However, the cutoff value of PG I and PG I/II ratio can be affected by several factors in determination of AG. Especially, *H. pylori* infection status could affect PG level. Age and sex are also confounding factors.⁵⁷ Several methods can be used to measure serum PG level including immunoradiometric assay (PG I/II RIA BEAD; Dainabot, Tokyo, Japan), latex enhanced turbidimetric immunoassay, enzyme-linked immunosorbent assays (Bihit ELISA kit; Biohit, Helsinki, Finland). The normal value of PG levels could be different depending on the test method. In addition, the optimal cutoff value for AG and gastric cancer screening could be different in different countries. For example, a Korean study showed that a PG I \leq 70 ng/mL produced a sensitivity of around 80% for detecting corpus AG and/or IM, but a very low specificity of around 30%.⁶²

4. *H. pylori* serology

During the progression of *H. pylori* infection, as AG and IM progress, the milieu of gastric mucosa works against the survival of *H. pylori* and it results paradoxically in spontaneous disappearance of *H. pylori*. That is, the serologic reversion of *H. pylori* in patients with AG and IM means that the aggravation of AG and IM. Given this background, the usefulness of *H. pylori* serology to additionally select high risk group for gastric cancer in individuals with low PG level has been widely reported. Japanese studies that analyzed risk of gastric cancer according the serum PG level and *H. pylori* serology status consistently reported that hazard ratios for gastric cancer were higher in severely atrophic *H. pylori*-negative cases than less atrophic *H. pylori*-positive cases (8.2 vs 6.0,⁶³ 131.98 vs 2.77,⁶⁴ and 61.85 vs 14.85⁶⁵). In a cohort of 4,655 healthy asymptomatic subjects, in whom serum PG and *H. pylori* antibody titer had been measured and was followed for up to 16 years, the authors reported that serum levels of PG and *H. pylori* antibody titer provide indices of cancer development (in order of lowest to highest risk of gastric cancer development: *H. pylori*-negative/AG-negative, *H. pylori*-positive/AG-negative, *H. pylori*-positive/AG-positive, and *H. pylori*-negative/AG-positive).⁶⁶ However, another Korean study concluded that the risk of gastric cancer was higher in patients with a low PG ratio and *H. pylori*-positive than in those with a low PG ratio and *H. pylori*-negative (OR, 5.52, 95% CI, 2.83 to 10.77 vs OR, 2.04, 95% CI, 0.58 to 7.19).⁶² Therefore, additional studies are required in more various countries.

5. Trefoil factor 3

Trefoil factors (TFFs) that consist of TFF1, TFF2, and TFF3 are highly expressed in tissues containing mucus-producing cells. They play key roles in the maintenance of mucosal integrity and oncogenic transformation, growth, and metastatic extension of solid tumors.⁶⁷⁻⁶⁹ TFF3 is expressed in the goblet cells of the small and large intestine, as well as IM in the stomach.⁷⁰⁻⁷³ In Japan, emerging data indicate that serum TFFs, especially TFF3, could be potential biomarkers for gastric cancer risk. In one study conducted in 192 gastric cancer patients and 1,254 noncancer controls, when serum PG I <70 and PG I/II ratio <3 was the cutoff point, the sensitivity and specificity for predicting gastric cancer was 67% and 82%, respectively, whereas a combination of TFF3 and serum PG test showed a sensitivity of 80% and specificity of 80% in predicting gastric cancer.⁷⁴ In another study conducted in 183 gastric patients and 280 healthy controls, using 3.6 ng/mL as a cutoff level of TFF3, the OR for gastric cancer was significantly increased (OR, 18.1; 95% CI, 11.2 to 29.2) and the sensitivity and specificity for predicting gastric cancer were 80.9% and 81.0%, respectively.⁷⁵ When compared with the receiver operating characteristic curves of the PG I/II ratio, TFF3 showed better positive and negative predictive values for gastric cancer screening. In addition, in contrast to PG,

TFF3 values were not considerably affected by *H. pylori* status, eradication, and aging.⁷⁶

However, similar to the serum PG test, serum TFF3 has a limitation in predicting the presence of diffuse-type adenocarcinoma. The sensitivity of serum PG test was poor in diffuse-type cancer (53.8%) and the sensitivity of TFF3 in diffuse-type adenocarcinoma were higher by 10% (63.5%) than that of serum PG test, but were still low.⁷⁴

Although the data has been confined only in Japan and is limited in predicting diffuse-type adenocarcinoma, serum levels of TFF3 might be a better nonendoscopic biomarker of gastric cancer than PG alone and a test for the combined levels of serum PG and TFF3 could improve gastric cancer screening. Further large studies are needed.

MANAGEMENT OF HIGH RISK GROUP FOR GASTRIC CANCER

At the present time, there are no unified global clinical guidelines regarding the definition and management of high risk group for gastric cancer.⁷⁷ However, considering that AG and IM have the highest OR for gastric cancer development among many risk factors, we could define individuals with AG and IM as being at high risk for gastric cancer. These individuals could be managed based mainly on two strategies. One is to reverse these premalignant lesions using a method like *H. pylori* eradication, or at least to stop progression of these premalignant lesions to gastric cancer. Another is to diagnose gastric cancer early in this high risk group.

1. *H. pylori* eradication for primary gastric cancer prevention

The hypothesis that *H. pylori* eradication is effective for gastric cancer prevention originated from epidemiological and interventional studies conducted in animals. Thereafter, observational studies in human were reported.⁷⁸ However, there are many controversies about the results of randomized controlled trials regarding an association between *H. pylori* eradication and gastric cancer development.

1) *H. pylori* eradication in the general population

In the early 2000s, Uemura *et al.*⁷⁹ reported that when 1,526 *H. pylori*-infected patients were prospectively followed-up for a mean of 7.8 years, gastric cancers developed in only *H. pylori*-infected patients. Thereafter, Wong *et al.*⁸⁰ reported that when they randomly assigned *H. pylori*-infected participants to receive *H. pylori* eradication treatment or placebo and followed-up for 7.5 years, *H. pylori* eradication significantly decreased the development of gastric cancer in subjects without AG and IM in the subgroup analysis. Several years later, a meta-analysis was performed regarding six randomized controlled trials that compared eradication treatment with no treatment in *H. pylori*-positive patients and assessed gastric cancer or progression of

pre-malignant lesions during follow-up.⁸¹ The authors concluded that *H. pylori* eradication decreases the RR of gastric cancer to 0.65 (95% CI, 0.43 to 0.98). However, in this meta-analysis, studies regarding *H. pylori* eradication in patients who received ESD for early gastric cancer (EGC) as well as in general population were included. The most recent study regarding mass eradication of *H. pylori* infection in the general population is from Taiwan.⁸² The authors compared the incidence of gastric cancer between approximately 5,000 *H. pylori*-infected patients over 30-years-of-age who received eradication therapy (2004–2008) and population before chemoprevention (1995–2003). The effectiveness of eradication therapy in reducing gastric cancer incidence was 25% (RR, 0.753; 95% CI, 0.37 to 1.52). These results generated global interest.

2) *H. pylori* eradication in AG and IM

Guidelines in Asia^{83–85} and Europe⁷⁸ recommend *H. pylori* eradication in patients with AG and IM. There have been several reports showing that *H. pylori* eradication can regress AG and IM,^{86,87} and *H. pylori* eradication is effective in diminishing the progression of IM.⁸⁸ The results of a meta-analysis including eight studies evaluated the long-term effects of *H. pylori* eradication on gastric histology; *H. pylori* eradication could improve AG but could not reverse IM.⁸⁹ In the aforementioned Taiwanese study, mass eradication of *H. pylori* infection led to a significant reduction in AG but could not significantly decrease IM.⁸² In addition, the aforementioned randomized controlled trial of Wong *et al.*⁸⁰ showed *H. pylori* eradication decreased gastric cancer development only in patients without premalignant lesions like AG and IM. These results imply that *H. pylori* eradication might be ineffective in those at high risk of gastric cancer.⁸⁰ A test-and-treat approach to *H. pylori* infection in younger people before the development of AG and IM could be more effective to prevent gastric cancer.⁹⁰ Indeed, since 2013, the Japanese National Health Insurance system expanded the application of medical insurance of *H. pylori* eradication to all patients with chronic gastritis.

Because a considerable fraction of patients in whom gastric cancer has already developed display advanced stage AG and IM, determining the incidence of metachronous gastric cancer in these patients after *H. pylori* eradication could indirectly predict the effect of *H. pylori* eradication on AG and IM. A retrospective study from Japan reported that *H. pylori* eradication in patients undergoing endoscopic resection for EGC reduces the incidence of metachronous gastric cancer.⁹¹ Thereafter, Fukase *et al.*⁹² reported that the OR for metachronous gastric carcinoma was 0.35 (95% CI, 0.16 to 0.78; $p=0.009$) in the *H. pylori*-eradication group compared to the control group among *H. pylori*-positive gastric cancer patients who underwent ESD. This served as the basis for recommending *H. pylori* eradication in EGC patients in Japan.⁸⁴ However, a succeeding retrospective study in Japan showed that *H. pylori* eradication does not reduce the incidence

of metachronous gastric cancer in patients underwent ESD for EGC during long-term follow-up.⁹³ The results of a randomized controlled trial regarding the effects of *H. pylori* eradication on the incidence of metachronous gastric cancer in 901 patients who underwent endoscopic resection of gastric tumors was recently published in Korea.⁹⁴ During a median follow-up of 3 years, the incidence of metachronous gastric cancer was not significantly different in the *H. pylori*-eradication and control groups. Additional studies are needed regarding the effect of *H. pylori* eradication in patients with AG and IM.

2. Surveillance for early detection of gastric cancer

Examination for early detection of gastric cancer is largely divided into mass screening for general population and surveillance for high risk individuals. Population-based screening for gastric cancer in Asia is currently done in Korea, Japan, and Matsu island of Taiwan. Korea and Japan have been conducting screening for gastric cancer in every individual over 40-years-of-age.^{95,96} On Matsu island, surveillance endoscopy is performed only in individuals with positive results of anti-*H. pylori* IgG, PG I, and II tests.⁹⁷ Asia-Pacific consensus guidelines on gastric cancer prevention does not suggest unified program and just recommends to continue gastric cancer surveillance based on each national guidelines, like the aforementioned programs.⁹

In Japan, around 1960, gastric cancer screening using photofluorography was started in Miyagi prefecture. Since 1983, gastric cancer screening was introduced for all residents aged 40 years and over.⁹⁵ The fact that while the reported incidence of EGC in Japan is 40%, the reported incidence of EGC in Europe is only 15% indirectly supports the effect of mass screening for early detection of gastric cancer.⁹⁸

In Korea, since 1999, the National Cancer Screening Program recommended esophagogastroduodenoscopy (EGD) or upper gastrointestinal series conducted biannually for individuals over 40-years-of-age. The fact that the proportion of EGC is over 80% among patients diagnosed as gastric cancer in 18,414 individuals who underwent EGD for health check-up also supports the effect of mass screening for gastric cancer.⁹⁹ However, lead-time bias and length bias should be considered in the analysis

of the effect of mass screening for cancer.¹⁰⁰ Therefore, the effect of mass screening for gastric cancer should be proven ultimately by reduction of mortality rate by gastric cancer. In a historical cohort study that compared the RR of gastric cancer death between 2,192 participants examined by EGD and 9,571 who was not examined by EGD or X-ray in Japan, the RR for gastric cancer death within 10 years in the examined group was 0.35 (95% CI, 0.14 to 0.86).¹⁰¹ However, long-term follow-up studies are needed.

In addition, very few studies have addressed the optimal interval of endoscopic screening for gastric cancer and no unified guideline exists. In a study in which population-based screening using EGD was done twice at a 5-year interval in China, mortality from gastric cancer was not different from expected values.¹⁰² In contrast, in Japanese study, the 5-year survival rate for patients who had undergone EGD within 2 years before the detection of gastric cancer was significantly higher than that for patients who had either undergone no EGD or had had EGD more than 2 years before the detection of gastric cancer (96.5% vs 71.0%, $p < 0.01$).¹⁰³ However, the survival rates were not significantly different between patients who had undergone EGD within 1 year before the detection of gastric cancer and patients who had undergone EGD more than 1 year and within 2 years. These results have served as the basis for recommending that the optimal interval for endoscopic gastric cancer screening should be 2 years. This 2-year endoscopic mass screening program was also proven to be cost-effective in moderate to high risk population when simulation was performed using a Markov model.¹⁰⁴ In a study that analyzed patients diagnosed with gastric cancer in the Korean National Cancer Center screening program, repeated endoscopic screening within 2 years decreased the incidence of gastric cancer and endoscopic resection could be applied to more patients who underwent EGD screening within 2 years.⁹⁹

Because there is still a controversy about effect of mass screening for gastric cancer, a surveillance strategy for high risk group of gastric cancer is more difficult. However, if we postulate that endoscopic screening for gastric cancer in general population has a positive effect on early detection of gastric

Table 3. Proposed Intervals of Surveillance Endoscopy in the High Risk Group for Gastric Cancer

Author (year)	Country	Type of article	Indication of surveillance	Proposed surveillance interval, yr
Busuttill <i>et al.</i> (2009) ¹¹⁰	Australia	RA	IM	1–3
Yoon <i>et al.</i> (2012) ¹⁰⁵	Korea	OA	Severe IM	1
Chung <i>et al.</i> (2012) ¹⁰⁶	Korea	OA	IM	1
Zullo (2012) ¹⁰⁷	Italy	RA	IM	2–3
			High risk IM*	1
Dinis-Ribeiro <i>et al.</i> (2012) ³⁸	Europe	GL	Extensive AG and/or IM	3

RA, review article; IM, intestinal metaplasia; OA, original article; GL, guideline; AG, atrophic gastritis.

*(1) IM extension >20%; (2) the presence of incomplete type IM; (3) first-degree relative of gastric cancer patients; and (4) smokers.

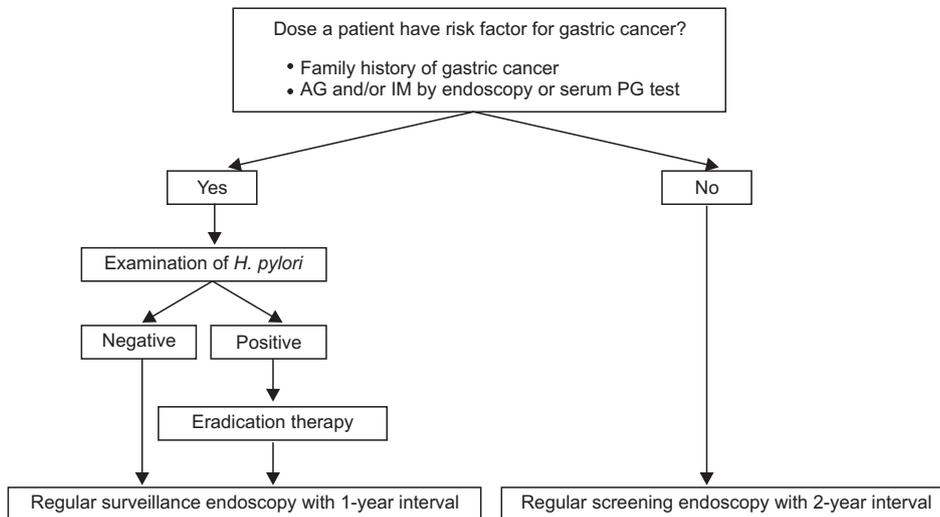


Fig. 1. Proposed strategy for managing high risk group for gastric cancer in Korea.

AG, atrophic gastritis; IM, intestinal metaplasia; PG, pepsinogen; *H. pylori*, *Helicobacter pylori*.

cancer and mortality reduction by gastric cancer, surveillance in those at high risk for gastric cancer would be expected to be more beneficial. In addition, the optimal interval of surveillance endoscopy in the high risk group should be equal or shorter than that in the general population. Proposed intervals of surveillance endoscopy in those at high risk of gastric cancer are summarized in Table 3.

A recent Korean study that analyzed 415 gastric cancer patients, in a subgroup of patients with severe IM, the ratio of EGC was higher among patients who had undergone endoscopic screening within 1 year before being diagnosed with gastric cancer than among patients who had not done it within the same period (66.7% vs 35.5%, $p=0.047$). In addition, the proportion of patients who underwent ESD was higher in among patients who had undergone endoscopic screening within 1 year before being diagnosed with gastric cancer (26.7% vs 0%, $p=0.008$). Therefore, the authors concluded that endoscopic screening for gastric cancer at 1-year intervals would be beneficial for patients with severe IM.¹⁰⁵ Another Korean study conducted in a healthcare center reported that proportion of EGC was higher in an annual screening group than in a biennial screening group (98.6% vs 80.7%, $p<0.01$) and endoscopic resection was performed more frequently in the annual screening group (56.9% vs 33.3%, $p=0.02$). This study also suggested that 1-year interval surveillance may be useful for high risk subpopulations with IM.¹⁰⁶ However, the risk for gastric cancer could vary with extent, severity and type of IM. A recent review article proposed that annual endoscopic surveillance should be justified in IM patients with at least one of following conditions: (1) IM extension >20%; (2) presence of incomplete type IM; (3) first-degree relative of gastric cancer patients; and (4) smokers.¹⁰⁷ The authors suggested surveillance with 2 to 3 years interval in the remaining IM patients. However, this suggestion is based on the small cohort studies in England¹⁰⁸ and Italy.¹⁰⁹ An-

other review article reported that surveillance of patients with IM at a frequency of 1 to 3 years may be appropriate.¹¹⁰ Recent European guideline suggested that patients with extensive AG and/or extensive IM should be offered endoscopic surveillance every 3 years (evidence level 4).³⁸ Taken together, the level of evidence for these proposals about optimal surveillance for high risk group for gastric cancer is quite low. In addition, a recent systemic review reported that studies about whether endoscopic surveillance of premalignant gastric lesions is cost-effective or not presented conflicting results.¹¹¹

FUTURE DIRECTIONS

Gastric cancer is still leading cause of morbidity and mortality worldwide. To reduce the socioeconomic burden related to gastric cancer, it is very important to identify and manage those at high risk for gastric cancer. Because AG and IM are the most significant factors among many risk factors of gastric cancer, the first key strategy is to accurately select individuals with AG and IM. Then, we have to prevent these high risk group from progression to gastric cancer and to detect gastric cancer in early stage. We propose a strategy for managing those over 40-years-of-age at high risk of gastric cancer in Korea (Fig. 1). This proposal was derived from expert opinion. Yet, evidence supporting some step of this strategy is somewhat low. For example, although several methods to select high risk group for gastric cancer have been developed, there is no gold standard method yet. In addition, whether *H. pylori* eradication could reverse AG and IM and prevent progression of AG and IM is still uncertain. Endoscopic surveillance in high risk group for gastric cancer would be expected to be beneficial. However, prospective studies in a large population are needed to determine optimal surveillance interval and to develop evidence-based strategy for managing high risk group for gastric cancer in Korea.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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