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Gastric Cancer Risk Diagnosis and Prevention in Subjects with *Helicobacter pylori*-related Chronic Gastritis

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1. Introduction

Helicobacter pylori (HP) is recognized as a major pathogenic factor for persistent inflammation in the human stomach (Dooley et al., 1989; Marshall & Warren, 1984). In 1994, the International Agency for Research on Cancer (IARC) classified HP infection as a definite class I carcinogen (International Agency for Research on Cancer (IARC), 1994). HP triggers chronic inflammation of the infected stomach mucosa and is considered a major risk factor for gastric cancer (GC) and associated precursor lesions. Long-lasting inflammation in the stomach mucosa leads to a cascade of molecular and morphological changes, representing the gastritis-atrophy-metaplasia-dysplasia-cancer sequence (Correa, 1992). The HP infection rate is higher in Japan than in Western countries, with nearly all cases of GC occurring in subjects with underlying HP-related chronic gastritis. HP infection is widely accepted as a major risk factor for the development of GC and its precursor lesions, based on extensive evidence derived from many studies (Blaser et al., 1995; EUROGAST Study Group, 1993; Forman et al., 1991; Hirayama et al., 1999; Honda et al., 1998; Huang et al., 1998; Nomura et al., 1991; Parsonnet et al., 1991; Shimizu et al., 1999; Sipponen et al., 1992; Sugiyama et al., 1998; Talley et al., 1991; Tokieda et al., 1999; Uemura et al., 2001; Watanabe et al., 1998; Zheng et al., 2004).

However, in countries such as Japan, where the HP infection rate is high, prediction of GC risk based solely on the presence or absence of HP infection does not offer sufficient specificity. Elucidation of groups at high risk based on the natural history of GC is clearly necessary. The identification of useful markers of GC risk is thus hoped for. Evaluating HP-related chronic gastritis and determining which subjects are at high risk for developing GC is very important, and would likely increase the efficacy of GC screening by endoscopic or other examinations (Enomoto et al., 2010a; Mukoubayashi et al., 2007; Ohata et al., 2005), and strategic approaches to metachronous multiple GC after endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) performed as minimally invasive treatment for early GC (Gotoda, 2007; Kakushima & Fujishiro, 2008; Nakajima et al., 2006). In addition, in terms of GC prevention, it has become clear that HP-related chronic gastritis cannot be ignored as an origin of carcinogenesis.

Here, we discuss the significance of serum pepsinogen (PG) as a marker of GC risk and GC high-risk groups based on HP-related chronic gastritis. We also discuss the prevention for individuals with HP-related chronic gastritis.

2. GC risk diagnosis based on the natural history of HP-related chronic gastritis

Novel risk markers to identify GC high-risk groups based on a detailed natural history of HP-related chronic gastritis have long been awaited. In this section, we discuss the emerging significance of serum PG as a GC risk marker for more precise identification of GC high-risk groups.

2.1 Serum PG test

HP-related chronic gastritis usually starts in the antrum and expands proximally towards the body of the stomach (Kimura, 1972; Tatsuta et al., 1973). As several studies dealing with endoscopic biopsies or chromoendoscopic testing have found that progression of chronic atrophic gastritis (CAG) increases the risk of cancer (Meister et al., 1979; Sipponen et al., 1985; Siurala et al., 1966; Tatsuta et al., 1993; Testoni et al., 1987), accurate and reliable evaluation of the extent of CAG is considered important for identifying individuals at high risk of cancer. However, accurately diagnosing the extent of CAG based on a few biopsy samples is difficult, because CAG together with intestinal metaplasia is a multifocal process. Furthermore, histological diagnosis of gastric atrophy depends on subjective judgment without a gold standard (Guarner et al., 1999; Plummer et al., 1997). A test for CAG progression that is more convenient, free of discomfort or risk, economical and based on objective parameters is needed.

PG is the inactive precursor of pepsin, a digestive enzyme specifically produced in the stomach. Immunologically, two isozymes exist (Kageyama, 2003). PGI is produced by chief cells and mucus neck cells of the gastric fundic glands. In contrast, PGII is produced not only by chief cells and mucus neck cells, but also in cardiac glands, pyloric glands, and Brunner's glands, with localization of producing cells in a wide range from the stomach to the duodenum. The majority of PG produced (about 99%) is secreted in the stomach lumen and functions as a digestive enzyme. However, a small amount of PG (about 1%) is also present in blood and can be evaluated by measuring serum PG levels. Serum PG levels are generally agreed to reflect the morphological and functional status of the stomach mucosa (Hirschowitz, 1957; Samloff et al., 1982).

In an endoscopic study with Congo red staining, we have shown a strong correlation between an increase in glandular boundary, associated with diagnosed progression of gastric mucosal atrophy, and stepwise reductions in serum PGI levels and the PGI/PGII ratio (**Fig. 1**) (Miki et al., 1987). In other words, by measuring serum PGI and the PGI/II ratio, the progression of CAG, which is involved in GC carcinogenesis, can be objectively evaluated (Ichinose et al., 2001). In addition, during HP infection, serum PGI and PGII increase, and the PG I/II ratio decreases. These findings are improved after eradication treatment (Furuta et al., 1997) and are useful as gastric mucosal inflammatory markers.

Several criteria are used in the serum PG test. As criteria for GC screening, the combination of PGI ≤ 70 ng/ml and PGI/II ratio ≤ 3.0 , as a reference value by Miki et al., is widely accepted (PG index 1+) (Ichinose et al., 2001; Watanabe et al., 1997). Values lower than this

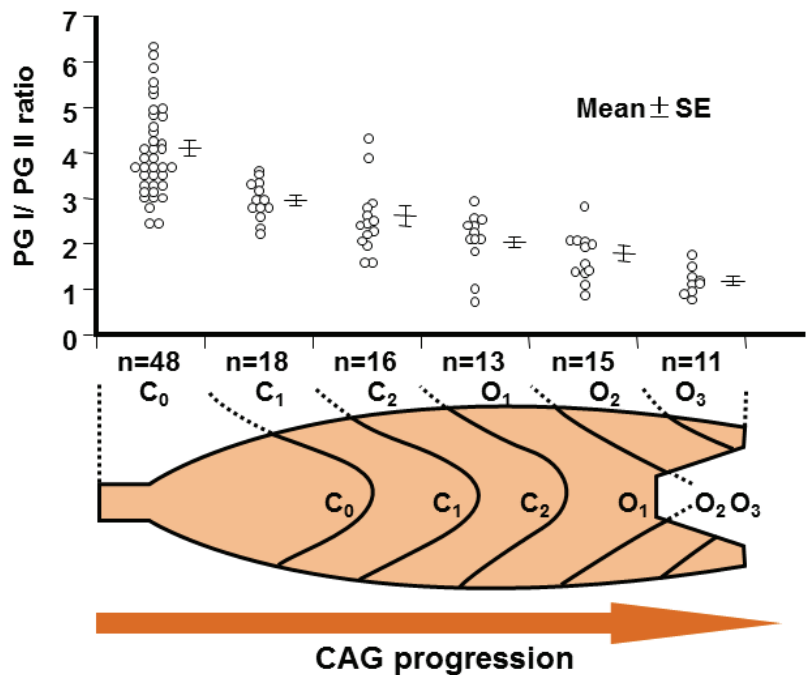


Fig. 1. Relationship between serum pepsinogen (PG)I/PGII ratio and progression of chronic atrophic gastritis (CAG). With atrophic changes in the gastric mucosa progressing from the pyloric glands to more proximally, the serum PGI/II ratio decreases, reflecting an associated loss of PG-producing cells. CAG, chronic atrophic gastritis; SE, standard error.

reference value are considered PG-test positive. In addition to this reference value, to identify more severe CAG progression, criteria of $\text{PGI} \leq 50 \text{ ng/ml}$ and $\text{PGI/II ratio} \leq 3.0$ (PG index 2+), and $\text{PGI} \leq 30 \text{ ng/ml}$ and $\text{PGI/II ratio} \leq 2.0$ (PG index 3+) are also used. Since 1992, when PG assay kits became commercially available, a number of screening services provided by workplaces or community health services have adopted this serum test as a filter test (Hattori et al., 1995; Kitahara et al., 1999; Kodoi et al., 1995; Miki et al., 1993; Miki et al., 2003; Ohata et al, 2005; Yoshihara et al., 1997). However, the long-term prognosis of subjects with extensive CAG identified by PG filter test is not fully known.

2.2 Detection accuracy of GC using the serum PG test

We conducted a large-scale cohort study spanning more than 10 years in Wakayama Prefecture, Japan, and identified groups at high risk for GC (Ohata et al., 2004; Yanaoka et al., 2008a; Yanaoka et al., 2008b). Based on the results, accuracy of each criteria of the serum PG test for GC that occurred during the observation period was evaluated (Yanaoka et al, 2008a). Accuracy of the criteria is shown in **Table 1**. For the most favorable criteria (PG index 1+), sensitivity was 58.7%, specificity was 73.4%, and positive predictive value was 2.6%. Compared to a meta-analysis of PG test sensitivity (Dinis-Ribeiro et al., 2004), these results were poor, particularly in terms of sensitivity.

As a reason for these poor results, the presence of GC easy to detect by barium X-ray, and GC easy to detect by the serum PG test, was cited (Ohata et al, 2005). In the above-mentioned meta-analysis, many of the previously reported cases that were reviewed were from studies in populations in which GC screening by conventional barium X-ray had been conducted over a period of many years. In other words, that study reviewed results for GC

	Serum PG test criteria		
	PGI ≤70 and PGI/II ≤3 [PG index 1+]	PGI ≤50 and PGI/II ≤3 [PG index 2+]	PGI ≤30 and PGI/II ≤2 [PG index 3+]
Meta-analysis of reported cases (Dinis-Ribeiro et al., 2004)			
Pooled sensitivity (95%CI)	77.3% (69.8-83.8)	68.4% (59.1-76.8)	51.9% (40.3-63.5)
Pooled specificity (95%CI)	73.2% (72.8-73.6)	69.3% (66.6-70.0)	84.4% (83.7-85.0)
Our results (Yanaoka et al., 2008a)			
Sensitivity (95%CI)	58.7% (45.6-70.8)	49.2% (36.5-62.0)	27.0% (16.9-39.9)
Specificity (95%CI)	73.4% (72.1-74.6)	80.5% (79.4-81.6%)	92.0% (91.3-92.8)

PG, pepsinogen.
CI, confidential interval.

Table 1. Comparison of accuracy for each criterion in the serum PG test.

detection just after introduction of the serum PG test, over a short period, and targeting a population in whom GC was difficult to detect by barium X-ray, i.e., those in whom GC was easy to detect by the serum PG test. On the other hand, GC cases just after introduction of the serum PG test were excluded from our study, and observation was over a long period of 10 years. Accordingly, results for the detection of GC occurring during the observation period were more rigorously evaluated, and thus more correctly reflective of the accuracy for detecting GC by the serum PG test. Based on the above results, using the serum PG test alone for GC screening has limitations. A more elaborate system must therefore be developed, including for GC screening in PG test-negative cases.

2.3 GC risk in a serum PG test-positive group

Previous studies have examined the accuracy of the serum PG test as a filter test for endoscopy. Recently, as part of an investigation into the natural history of GC occurrence, we evaluated GC risk in populations identified by each criteria for the serum PG test (Yanaoka et al, 2008a). In a population of middle-aged healthy men, in an atrophy-negative group, the annual incidence of GC was 0.07%. In contrast, annual incidence was 0.28% in the PG index 1+ group, 0.32% in the PG index 2+ group, and 0.42% in the PG index 3 +group, showing significant stepwise increases in GC incidence with CAG progression (**Fig. 2**) Based on these results, PG test-positive groups, as assumed, are high-risk groups for GC. In other words, an individual who is serum PG test-positive, even if GC is not currently detectable, still has a high possibility of developing GC in the future. Careful monitoring with detailed testing is clearly indicated in such subjects. This again demonstrates the usefulness of the PG test as a marker of high risk for GC.

2.4 Natural history of HP-related chronic gastritis and GC risk

In addition to the serum PG test, the natural history of HP-related chronic gastritis and associations with GC risk have been examined by evaluating HP infection, as the major cause of onset and progression of chronic gastritis in Japan (Ohata et al, 2004; Yanaoka et al, 2008b). HP infection is diagnosed using anti-HP antibody titers, which, like the serum PG test, is a blood test that is easy to perform. The stages of HP-related chronic gastritis, from

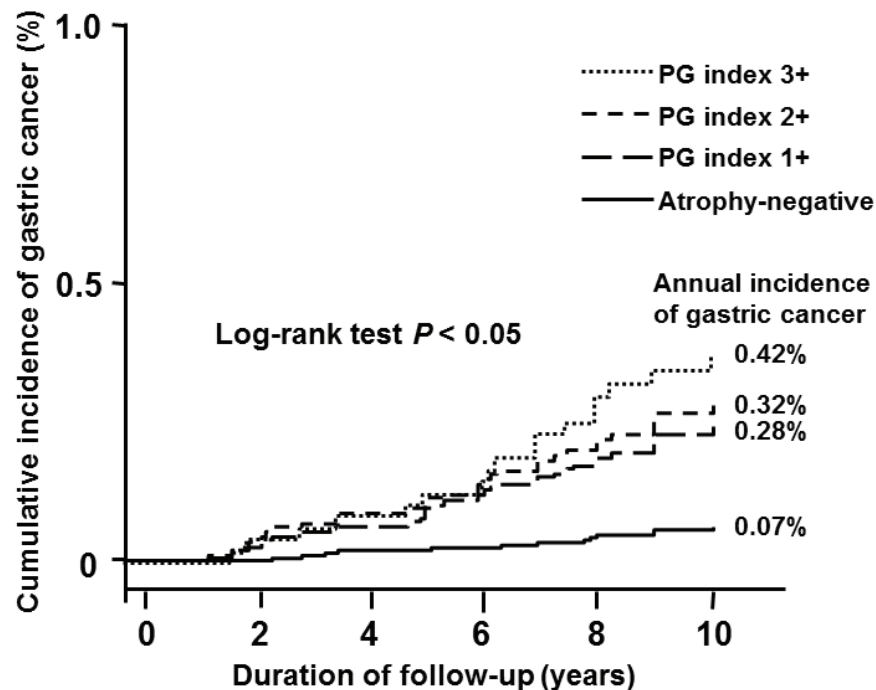


Fig. 2. Kaplan-Meier analysis of gastric cancer development in subjects classified using the criteria of the serum pepsinogen (PG) test. Among middle-aged healthy men, annual incidence of gastric cancer is shown for each population identified using various criteria for the serum PG test. Progression of chronic atrophic gastritis showed a significant stepwise increase in the incidence of gastric cancer.

the onset of HP infection to development of atrophic gastritis, can be classified based on a combination of both serum blood tests: Group A [HP(-), PG(-)], Group B [HP(+), PG(-)], Group C [HP(+), PG(+)], and Group D [HP(-), PG(+)]. Group A comprised HP non-infected healthy subjects. Group B showed established HP infection, but without extensive CAG. Group C had extensive CAG. Group D had severe intestinal metaplasia due to progression of CAG, but HP had been spontaneously eliminated, representing so-called metaplastic gastritis.

The natural history of HP-related chronic gastritis from the onset of HP infection can be shown to progress from each stage: A→B→C→D. Based on a follow-up study, the annual incidence of GC for each group using this stage classification was: 0% for Group A (no occurrence of GC during 10 years in this group); 0.11% for Group B (GC in 1 per 1000 patients per year); 0.24% for Group C (GC in 1 per 400 patients per year); and 1.31% for Group D (GC in about 1 per 80 patients per year). Based on these data, with progression in stage of HP-related chronic gastritis, a stepwise increase is seen for GC incidence (Fig. 3). Similar results were reported by Watabe et al. (Watabe et al., 2005). During the 10-year follow-up study, all patients who developed GC were HP infection-positive. These results showed that in Japan, almost all cases of GC are associated with HP-related chronic gastritis. Theoretically, based on this fact, not only a GC high-risk group, but also a GC low-risk group (group A), can be identified. This is expected to contribute greatly to suitable and more intensive GC screening.

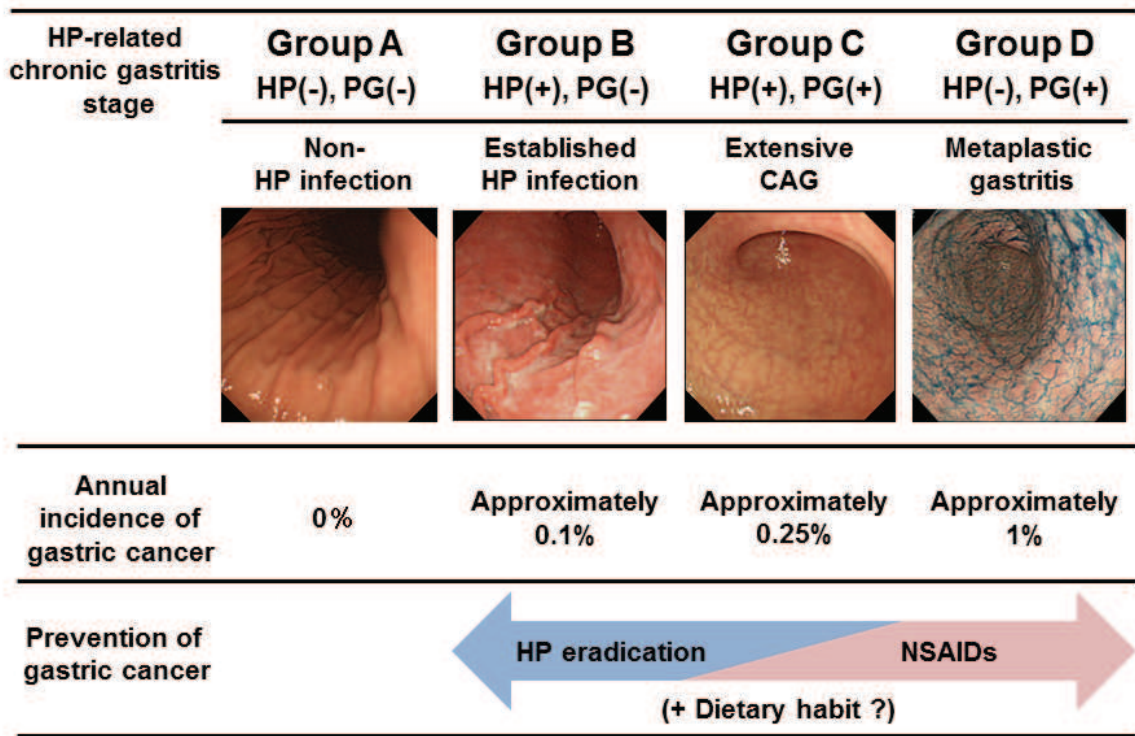


Fig. 3. Gastric cancer risk and prevention of gastric cancer based on *Helicobacter pylori* (HP)-related chronic gastritis stage. This shows the stage classification for HP-related chronic gastritis based on the serum pepsinogen (PG) test and HP antibodies. Among middle-aged healthy men, the annual incidence of gastric cancer showed a significant stepwise increase from Group A to Group D according to stage progression. Regarding gastric cancer prevention based on stage, in Group B, with mild atrophy, prevention of gastric cancer mainly by HP eradication can be expected. In Group D, with progression of atrophy and metaplastic gastritis, prevention of gastric cancer mainly by administration of non-steroidal anti-inflammatory drugs (e.g., cyclooxygenase 2 inhibitors) can be expected. In addition, prevention of gastric cancer may be possible with dietary habits.

2.5 Points in the diagnosis of GC risk using the serum PG test

The serum PG test is clearly a highly useful test for a GC risk marker. However, the occurrence of GC (particularly diffuse-type GC) in PG test-negative groups (group B in the stage classification for HP-related chronic gastritis) cannot be ignored. In our study, even when using the PG test criteria considered as the most balanced in terms of test accuracy (PG index 1+), the fact remains that about 40% of GC cases are PG test-negative. When diagnosing GC risk using the serum PG test, this fact must be carefully considered. We therefore carefully investigated GC occurrence in a PG test-negative group. Specifically, to evaluate GC incidence, we subdivided the PG test-negative group into 3 groups: α group (serum PGI ≤70 ng/ml and PGI/II >3); β group (serum PGI >70 ng/ml and PGI/II >3), and γ group (serum PGI >70 ng/ml and PGI/II ≤3). The results identified a new group at high risk of GC, with GC incidence in the γ group (high serum PGII levels and severe inflammation of the gastric mucosa) reaching 0.2%, predominantly involving undifferentiated GC (Yanaoka et al, 2008a). This rate in the γ group, although not necessarily high among the PG test-negative group, still indicates a subgroup that deserves

particular attention. In addition, a group with high HP antibody titer (a marker that, like serum PGII level, reflects severity of inflammation) showed higher incidence of GC compared to a low-titer group (Yanaoka et al, 2008b).

Among PG test-negative groups, in group A of the stage classification for HP-related chronic gastritis (PG test-negative and HP-negative), we observed no occurrence of GC over a 10-year follow-up period. However, some cautionary points must be considered in a confirmatory diagnosis of Group A status. First, with HP antibody assay kits showing low sensitivity, antibody titers may be negative despite prior HP infection. Second, in HP-negative cases after eradication therapy, it should be kept in mind that “although HP is negative, the risk of GC is not zero.” Third, risk assessment by the serum PG test cannot be applied in subjects with post-gastrectomy, with renal insufficiency, using proton pump inhibitors, or showing an acute gastric mucosal lesion (AGML). In addition, we have reported that in subjects with a PGI/II ratio ≤ 3.0 , serum PGI ≤ 30 ng/ml, or serum PGII > 30 ng/ml, the risk of GC is significantly higher (Yanaoka et al, 2008b). Based on these data, even among group A patients, if the PGI/II ratio is ≤ 3.0 or serum PGI is ≤ 30 ng/ml, endoscopy should be performed once to evaluate the possible presence of CAG.

3. Prevention of GC based on the natural history of HP-related chronic gastritis

The evaluation of HP-related chronic gastritis is especially important in the analysis of GC prevention. However, previous studies have not assessed the extent of coexisting CAG or have assessed it only with endoscopic findings and/or histopathology on endoscopic biopsy. In this section, we discuss the strategy of GC prevention according to the evaluation of HP-related chronic gastritis based on the serum PG test.

3.1 Prevention of GC by HP eradication

Many previous studies have been conducted on the inhibition of GC by eradication therapy for HP, a major factor in gastric carcinogenesis. HP eradication therapy has recently been shown to prevent metachronous cancer after endoscopic resection of early GC (Fukase et al., 2008). However, in several reports to date, the effects on prevention of GC have not been as clear-cut as the effects of HP eradication on prevention of peptic ulcers. The studies that found inhibitory effects on gastric carcinogenesis were often non-randomized studies with a short observation period of ≤ 5 years (Fuccio et al., 2007). Moreover, results have been mixed. For example, in studies of GC occurrence after HP eradication in groups with or without precancerous lesions (CAG or intestinal metaplasia), significant inhibition of GC in the without-precancerous-lesion group was reported (Take et al., 2007; Wong et al., 2004). On the other hand, absence of inhibition of GC, regardless of the presence or absence of precancerous lesions, has also been reported (You et al., 2006). In contrast, in an animal study using HP-infected Mongolian gerbils, inhibition of gastric carcinogenesis by HP eradication was clearly demonstrated (Tatematsu et al., 2007).

These study results suggest several points. First, inhibition of gastric carcinogenesis by HP eradication is not complete, and even after eradication, more than a few GC cases have been observed. Second, the earlier during infection that eradication therapy is started, the greater the inhibitory effect on GC. Third, after a duration has elapsed, irreversible changes due to HP infection develop, representing a “point of no return”. This suggests an attenuated

eradication effect. Fourth, HP infection promotes the proliferation and growth of cancer cells that have already developed (promoter effect). During long-term observation, clear-cut inhibition of gastric carcinogenesis by HP eradication is not seen, but eradication groups with shorter observation periods may display apparent inhibition of GC, with slower growth rates, and without growth of cancer that can be clinically diagnosed. Fifth, besides promoter effects on GC, HP infection, as previously described in detail, is also involved in gastric carcinogenesis mediated through the development and progression of CAG and intestinal metaplasia. To achieve a reduction in GC risk by eradication, in addition to HP elimination, improvement of CAG and intestinal metaplasia is necessary. Based on these points, when evaluating the prevention of GC by HP eradication, evaluation of the equivalence of GC risk in the eradication group and non-eradication group (control) is necessary. With regard to this point, in almost all previous studies, either evaluation of CAG progression has been lacking, or even if evaluated, endoscopic or histopathologic findings, with strong subjective elements, were used. We therefore conducted a 10-year follow-up study in middle-aged healthy adults in whom progression of atrophic gastritis was monitored by serum PG (Yanaoka et al., 2009). In that study, although non-randomized, both the HP eradication and control groups showed equivalence with regard to CAG progression (an important risk factor), in addition to major risk factors for GC such as age, gender, and smoking. In this study, no significant inhibition of GC was observed even with HP eradication. However, with assessment by the PG test, evaluation in the PG test-positive (extensive CAG) and PG test-negative (non-extensive CAG) groups showed that HP eradication in the PG test-positive group did not prevent GC, whereas HP eradication in the PG test-negative group only achieved significant inhibition of GC (Fig. 4). These results confirm the

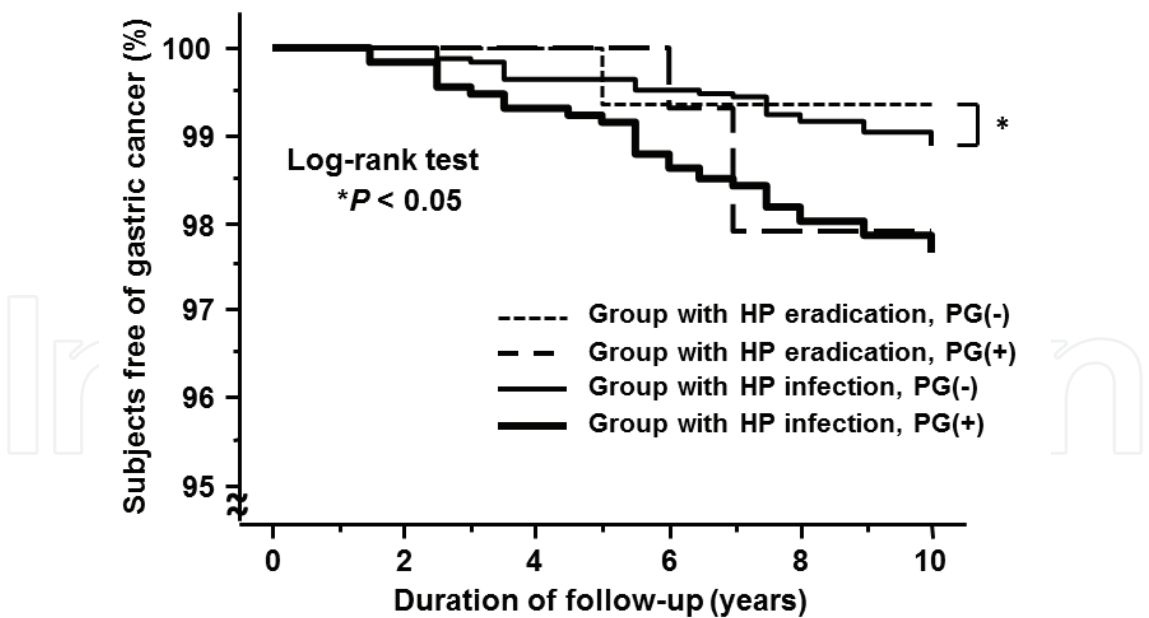


Fig. 4. Kaplan-Meier analysis of the proportion of subjects free of gastric cancer in the serum pepsinogen (PG) test-positive group and the PG test-negative group according to *Helicobacter pylori* (HP) infection status. In the serum PG test-positive group (extensive chronic atrophic gastritis (CAG)), no reduction in gastric cancer incidence was observed with HP eradication. Only the PG test-negative group (non-extensive CAG) showed a reduction in gastric cancer incidence with HP eradication.

previously mentioned results that assumed that no significant prevention of GC by HP eradication was achieved due to advanced CAG. This strongly suggests that in the majority of PG test-positive subjects, the stomach is past the “point of no return.” The significance of HP eradication thus lies in achieving: 1) a decrease in GC proliferation and growth rates by inhibiting the GC-promoting effects of HP; 2) inhibition of carcinogenesis by halting progression of CAG; and 3) inhibition of inflammation-based gastric carcinogenesis (particularly diffuse-type GC) by healing chronic active gastritis. In fact, our study also showed that diffuse-type GC can be significantly inhibited by HP eradication.

3.2 Chemoprevention of GC by NSAIDs

Although prevention of GC by HP eradication can be expected, from a more realistic perspective, the effectiveness may be somewhat limited. In particular, among patients with advanced CAG, the chemopreventive effects of HP eradication therapy alone are unlikely to be sufficient. In populations where inhibition of gastric carcinogenesis cannot be achieved by HP eradication therapy alone, chemoprevention with the use of non-steroidal anti-inflammatory drugs (NSAIDs) is promising as a treatment strategy. Cyclooxygenase (COX) is a rate-limiting enzyme of prostaglandin synthesis in the arachidonic acid cascade. Among COX isozymes, attention has been focused on inducible COX-2, which is expressed in inflammatory responses and cancer proliferation (Kujubu et al., 1991). COX-2 expression has been reported in many gastrointestinal cancers, including colorectal cancer (Eberhart et al., 1994), and research has been undertaken into the prevention of carcinogenesis by COX-2 regulation (Giardiello et al., 1993; Kawamori et al., 1998; Kune et al., 1988; Thun et al., 1991). With regard to COX-2 expression in the gastric mucosa, not only a high rate of COX-2 expression in GC cells, but also COX-2 expression in precancerous lesions such as CAG, intestinal metaplasia, and dysplasia has been reported (Sung et al., 2000). In a study of GC tissue types, a high rate of COX-2 expression was found in intestinal-type GC (Saukkonen et al., 2001). In a study of GC according to site, cancers of the gastric cardia showed decreased COX-2 expression compared to cancers of other gastric areas (Ratnasinghe et al., 1999). In epidemiologic and animal studies, long-term use of aspirin or other NSAIDs has been reported to decrease GC risk in a dose-dependent manner (Duan et al., 2008; Hu et al., 2004; Wang et al., 2003).

In a Mongolian gerbil model of chronic active gastritis, which closely resembles HP-related chronic gastritis in humans, we evaluated the effects of etodolac, a selective COX-2 inhibitor, after initiation with a low dose of N-methyl-N-nitrosourea, a chemical carcinogen (Magari et al., 2005). The results confirmed that treatment with etodolac early in HP infection completely inhibited gastric carcinogenesis, which usually occurs at a high rate. In this model, we confirmed that proliferation of gastric mucosal epithelial tissue was significantly inhibited by etodolac, and that the development of intestinal metaplasia, thought to be a precancerous lesion, was significantly inhibited. In addition, we conducted a clinical study of GC chemoprevention using a COX-2 inhibitor in patients with metaplastic gastritis (Yanaoka et al., 2010). This study, although non-randomized, included patients who had undergone endoscopic resection of intestinal-type GC with a background of metaplastic gastritis. The incidence of metachronous cancer was evaluated in etodolac and non-treatment groups during a mean observation period of 4.2 years. The diagnosis of metaplastic gastritis was based on serum testing, as previously described. Regarding HP-related chronic gastritis stage, these patients were classified as Group D [HP(-), PG(+)]. In this study, long-term treatment with etodolac as a selective COX-2 inhibitor effectively inhibited metachronous cancer development in curatively treated, early GC patients with

metaplastic gastritis. These results are in line with the results of our previous animal experiment using HP-infected Mongolian gerbils, indicating that etodolac can prevent stomach carcinogenesis involving the CAG-metaplasia-dysplasia-cancer sequence. Serious cardiovascular events, depending on the drug, have been reported with long-term administration of COX-2 inhibitors. Whether etodolac is the best choice requires further investigation. However, particularly among patients with extensive CAG, in addition to HP eradication therapy, aggressive chemoprevention using NSAIDs such as selective COX-2 inhibitors may effectively inhibit gastric carcinogenesis (Fig. 3).

3.3 Possible GC prevention by dietary habits

On the other hand, HP eradication therapy and chemoprevention using NSAIDs were not carried out in all subjects, as problems exist with adverse effects of HP eradication or chemoprevention, drug-resistant bacteria, and medical economics. Research into HP-related chronic gastritis and promoters and inhibitors of gastric carcinogenesis, and studies of alternative therapies, primarily in the form of functional foods, has thus been conducted. In the progression of HP-related chronic gastritis, besides HP virulence factors such as VacA and CagA (Hatakeyama, 2004), and host factors such as cytokine polymorphisms (El-Omar et al., 2000), environmental factors such as lifestyle and dietary habits have been shown to be involved. In particular, dietary factors have been highly implicated as the factors to which the gastric mucosa is most frequently and directly exposed. For example, high sodium intake increases gastric mucosal inflammation and the risk of gastric cancer (Nozaki et al., 2002; Shikata et al., 2006) and cigarette smoking is considered to be deeply involved in the transition of CAG to intestinal metaplasia and dysplasia (Kneller et al., 1992; Tredaniel et al., 1997), which are precancerous conditions, in a model of gastric carcinogenesis postulated by Correa (Correa and Houghton, 2007). On the other hand, epidemiologic and animal studies have found that vegetables, fruits, and green tea can inhibit gastritis and reduce gastric carcinogenesis (Kobayashi et al., 2002; Yu et al., 1995).

The Japanese apricot (JA) (*ume* in Japanese; *Prunus mume* Siebold et Zucc.), in extracted or pickled form, has long been empirically used in Japan as a folk remedy for gastrointestinal infections such as gastroenteritis. In an in vitro study, Fujita et al. reported that JA extract displayed bactericidal activity against HP (Fujita et al., 2002). In addition, in an animal study using Mongolian gerbils, Otsuka et al. showed in vivo anti-HP effects of JA extract, demonstrating inhibition of chronic gastritis in HP-infected Mongolian gerbils (Otsuka et al., 2005). Based on these reports, because of the presumably potent anti-HP effects of JA, we conducted a study on associations between regular consumption of JA and HP-related chronic gastritis (Enomoto et al., 2010b; Jones, 2010). As a result, we found that consumption of JA is effective in inhibiting HP-related active inflammation of the stomach and CAG progression, and that development of GC may be inhibited by JA intake. Of course, because dietary habits are greatly influenced by other lifestyle factors, depending on the population being studied, the effectiveness achieved in preventing GC may differ. However, promoting dietary habits that protect against GC, including JA intake, may be an ideal alternative strategy for GC prevention (Fig. 3).

4. Conclusion

In conclusion, based on the natural history of HP-related chronic gastritis from blood test data, including the serum PG test and HP antibodies, specific prediction of the risk of GC in

each individual is now possible. With this information, more effective strategies to prevent GC are becoming possible. These are anticipated to have clinical applications such as in more effective GC screening, and in establishing appropriate GC prevention.

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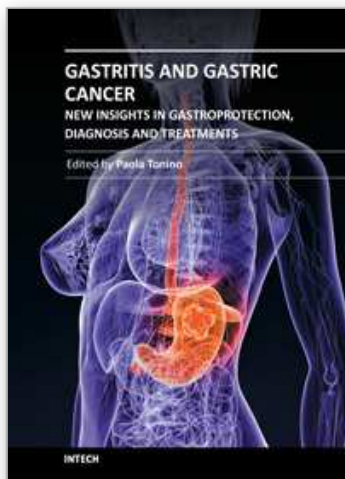
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Gastritis and Gastric Cancer - New Insights in Gastroprotection, Diagnosis and Treatments

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This book is a comprehensive overview of invited contributions on *Helicobacter pylori* infection in gastritis and gastric carcinogenesis. The first part of the book covers topics related to the pathophysiology of gastric mucosal defense system and gastritis including the gastroprotective function of the mucus, the capsaicin-sensitive afferent nerves and the oxidative stress pathway involved in inflammation, apoptosis and autophagy in *H. pylori* related gastritis. The next chapters deal with molecular pathogenesis and treatment, which consider the role of neuroendocrine cells in gastric disease, DNA methylation in *H. pylori* infection, the role of antioxidants and phytotherapy in gastric disease. The final part presents the effects of cancer risk factors associated with *H. pylori* infection. These chapters discuss the serum pepsinogen test, K-ras mutations, cell kinetics, and *H. pylori* lipopolysaccharide, as well as the roles of several bacterial genes (*cagA*, *cagT*, *vacA* and *dupA*) as virulence factors in gastric cancer, and the gastrokine-1 protein in cancer progression.

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