感染経路は家族内が主であり，特に母から子への感染が重要という報告が多い。また，保育施設や障害児施設などでの子どもどうしの感染も示唆されている。日本における感染経路は家族内8割（母から約7割，父から約1割），家族外感染は2割程度とする報告もある[3]。感染様式は生活環境や時代により異なる。胃以外で培養やPCR法で*H. pylori*が検出されたものは，歯垢，唾液，糞便，嘔吐物，井戸水などで，これらは感染を媒介する。疫学調査で母の悪心・嘔吐が頻繁であると子どもの感染率が高い，感染している家族が嘔吐を伴う胃腸炎症状を発症すると年少児の新規感染が多くなるという報告などからは*H. pylori*感染者が嘔吐・下痢を伴う病態では感染源となり，乳幼児が初感染を受けるという経路が推測できる。発展途上国では飲料水を介した感染が報告されており，日本も戦後の衛生環境の悪い状況では飲料水を介した感染が多かったと推測されるが，現在の日本では水道水など飲料水からの感染の可能性は極めて低いと考えられている。

3 感染診断法（表1）

内視鏡による生検組織を必要とするものと生検組織が必要でない検査法がある。検査法が複数であれば感染診断の精度はさらに高くなるが，各々の検査法には特徴があるため理解したうえで選択する。

1）内視鏡による生検組織を必要とする検査法

生検部位に関しては，成人では幽門前庭部大彎と胃体上部～中部大彎の2か

表1　*H. pylori*感染症の診断および除菌判定法

	感染診断	除菌判定
生検組織を必要とする検査法		
組織検査（鏡検法）	○	△*
ウレアーゼ試験	○	△*
培養法	○	△*
生検組織を必要としない検査法		
尿素呼気試験	○	○
便中抗原検査	○	○
抗体検査（血清，尿）	△**	×

*偽陰性に注意する。
**単一検査としては好ましくない。
除菌判定は偽陰性を避けるため治療終了後4週以降に実施する。
（文献4より引用）

所からの生検が望ましいとされている。

(1) 培養法

唯一の直接的証明法であり，薬剤感受性テストもできる。特異性は優れているが感度がやや落ちる。専用培地が必要で外注検査となる医療機関が多く，胃組織を検査機関に送付する際にも *H. pylori* 用の保存輸送用培地が必要であり，検査前に取り寄せておく。

(2) 迅速ウレアーゼ試験

迅速かつ簡便で精度は高い。胃生検組織中に含まれる菌のウレアーゼ活性(尿素→二酸化炭素＋アンモニア）を検出することにより間接的に *H. pylori* の存在を確認する。試薬は尿素と pH 指示薬を利用したものでアンモニアが生じることによって pH が上昇し，pH の変化に伴う指示薬の変化で診断する。陰性を確認するための時間は 30 分～3 時間である。

(3) 鏡検法

胃生検組織標本上で菌による組織変化と併せて形態学的にラセン状菌を検出し，同時に組織診断も可能であるが熟練が必要である。検査結果の保存性は高く，組織診断もできる。

2) 内視鏡による生検組織を必要としない検査法

(1) 尿素呼気試験 (UBT)(図)

内視鏡を使わない検査法のゴールドスタンダードとされ，*H. pylori* がもつ強いウレアーゼ活性を間接的に測定する方法である。^{13}C 尿素製剤を服用し，胃内に *H. pylori* が存在すれば尿素は直ちに胃内でアンモニアと $^{13}CO_2$ に分解され，$^{13}CO_2$ は呼気に排出される。服用後の呼気を採取し，服用前に採取した呼気中の $^{13}CO_2$ と比較し増加率から存在を診断する。検査の条件として呼気の採取と“うがい”ができることが必須であり，乳児では検査困難である。^{13}C 尿素製剤は現在 100 mg 錠剤のみであり，錠剤を飲めない場合は約 100 ml の水で溶解する。服用した ^{13}C 尿素がウレアーゼ活性を有する口腔内細菌と接触し，口腔内で $^{13}CO_2$ を発生し，偽陽性の原因となるため，^{13}C 尿素の除去目的で“うがい”が必要である。現在日本で市販されているのはユーピット錠® とピロニック錠® であるが，表面がフィルムコーティングされた錠剤 (ユーピット錠®) ではうがいの必要はない。水に溶解した場合は口腔内に残りやすく十分にうがいを行う。投与量は 12 歳未満 75 mg，12 歳以上は 100 mg を大まかな目安としているが全年齢 100 mg としても構わない。服用後の呼気はユーピット錠では

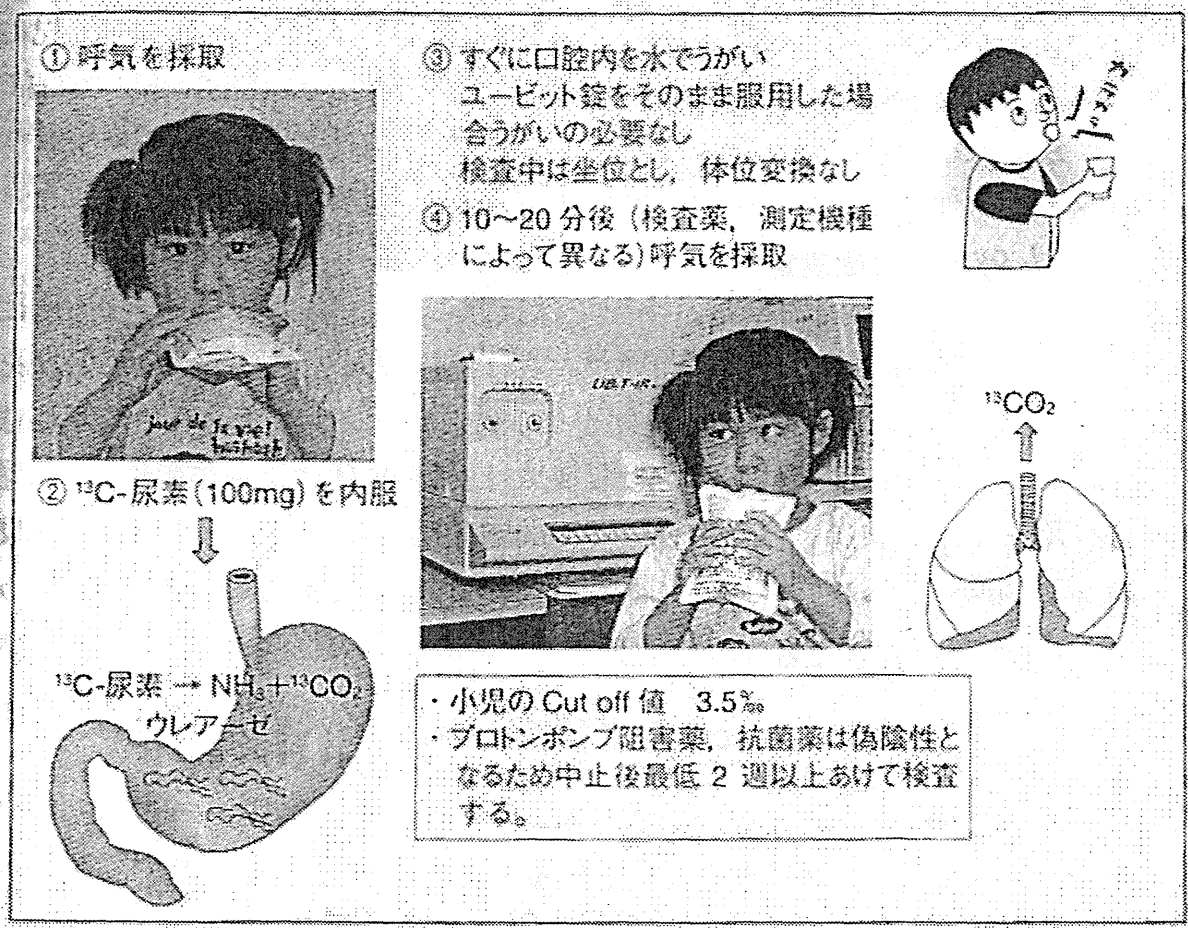

図　小児のUBT

20分後に，ピロニック錠®では服用10分後（質量分析法）あるいは服用15分後（赤外分光法）に採取する。成人では左側臥位5分の後に坐位と体位変換するが，小児では坐位のみで正確に診断できる。日本人小児の多施設研究結果ではカットオフ値を3.5‰とすると感度97.8%，特異度98.5%と報告されている。成人ではカットオフ値2.5‰が推奨されているので，われわれは2.5～3.5‰はgray zoneとして他の検査法を追加している。抗菌薬，ビスマス製剤や酸分泌抑制薬，特にプロトンポンプ阻害薬（PPI：オメプラゾール，ランソプラゾール，ラベプラゾールなど），抗ウレアーゼ活性のあるエカベトナトリウムなどの内服で偽陰性になるため，最低2週間は休薬し検査する。

(2) 便中抗原測定法

便を採取するだけという極めて非侵襲的，簡便な方法で，乳幼児，重度の障害児も同様に検査ができるという長所がある。小児においても成人と同じカットオフ値が用いられるが，抗菌薬の投与の影響については十分な検討はなく，UBTと同様に2週間程度の休薬後に検査することが望ましいと考えられる。現

在販売されているものはいずれもモノクローナル抗体を用いたもので，小児において90%以上の感度，特異度が報告されている。ELISA法(HpSA plus Meridian，テストメイトピロリ抗原EIA)，イムノクロマト法ではテストメイトラピッドピロリ抗原とイムノカードST HpSAが測定可能である。

(3) 抗*H. pylori*抗体測定

血清や尿を用いて測定できる。小児では抗原として用いられている菌株によってキット間で感度と特異度に差違がみられ，日本人から分離された菌株を使用したキットでは感度がよい。年少児（10歳未満）では感度がやや低く注意が必要である。乳児やγグロブリン投与後では受動抗体による偽陽性，乳幼児では免疫応答の未熟性による偽陰性などが問題となる。一方，小児に頻回に投与される抗菌薬の影響は受けず，特異度は良好であるためこれらの特性を知っていれば感染の目安となる。

4 どのような疾患で診断，治療するべきか

*H. pylori*感染児の多くは無症状である。小児期ヘリコバクター・ピロリ感染症の診断，治療，および管理指針[9]に記載された以下の疾患について除菌治療が考慮される。

1) 胃潰瘍，十二指腸潰瘍

わが国の小児では十二指腸潰瘍の約80%，胃潰瘍の約40%に*H. pylori*感染が証明される。初発・再発を問わず，除菌療法が治療の第一選択である。除菌治療により維持療法なしに潰瘍再発が抑制されることは世界的にコンセンサスが得られている。活動性潰瘍では，除菌治療後プロトンポンプ阻害薬などの酸分泌抑制薬の投与を行うことが望ましい。潰瘍の治癒確認は内視鏡検査で行い，検査時期は除菌判定も考慮し治療開始後8週前後が目安となる。

2) 慢性胃炎

内視鏡検査と組織検査により診断する必要があり，①症状改善を期待し本人および親が希望する，②胃粘膜の萎縮が証明される，③胃癌の家族歴を有する場合，除菌療法が考慮される。しかし，*H. pylori*慢性胃炎と腹部症状との関連について確立した見解はなく，除菌により症状の消失ないし改善が得られる保証はない。

表2　*H. pylori* 関連鉄欠乏性貧血の特徴

①患児の多くは腹痛などの消化器症状を訴えない。
②繰り返し便潜血検査などを行っても消化管出血が確認されない。
③鉄の摂取不足が認められない。
④内視鏡所見と生検による病理組織検査で *H. pylori* 胃炎が確認される。
⑤貧血が鉄剤による治療に不応である（鉄剤不応性）か，鉄剤に反応しても投与中止によって貧血が再燃する（鉄剤依存性）。
⑥鉄剤を補充しなくても *H. pylori* の除菌のみで貧血が改善されることもある。

（文献5より引用）

3）胃 MALT リンパ腫

MALT（mucosa-associated lymphoid tissue：粘膜関連リンパ組織）を発生母地とする低悪性度の悪性リンパ腫である。成人領域では除菌による胃 MALT リンパ腫の改善は 60～80％程度であり，現在では限局期の低悪性度リンパ腫の治療法の第一選択は *H. pylori* 除菌療法とされている。小児では報告が少ないが，*H. pylori* 感染が証明されれば除菌療法を考慮し，治療無効例には速やかに他の治療法を選択する。

4）蛋白漏出性胃症

除菌治療により血清蛋白値や内視鏡・病理所見の正常化がみられることがある。*H. pylori* 感染以外に原因が見出されない場合に実施する。

5）鉄欠乏性貧血（表2）[5]

小児期では *H. pylori* 関連疾患として重要である。特に 10 歳以降の年長児の原因不明の鉄欠乏性貧血児の約 60～70％が *H. pylori* 感染があり，除菌成功した症例では貧血が治癒し再発を認めない。スポーツ貧血との合併でさらに強い貧血をきたしたと思われる症例も多い。年少児の鉄欠乏性貧血における *H. pylori* 感染率は高くない。

6）血小板減少性紫斑病

成人の *H. pylori* 陽性慢性 ITP 患者の約半数が除菌後に血小板増加を認められることが明らかとなってきた。成人では慢性 ITP の確定診断後早期に感染診断を実施し，*H. pylori* 陽性例に対しての first-line 治療として除菌治療をすることは，EBM として確立されてきている。小児の効果についてはさまざまな報告が

表3　小児の除菌療法に用いられる主な薬剤と一般的な用量

	用量 (mg/kg/日)	最大量 (mg/日)
プロトンポンプ阻害薬		
ランソプラゾール*	1.5	60
オメプラゾール**	1.0	40
抗菌薬		
アモキシシリン	50	1,500
クラリスロマイシン	10～20	800
メトロニダゾール	10～20	500

プロトンポンプ阻害薬はいずれか1剤，抗菌薬は一次除菌療法としてアモキシシリン，クラリスロマイシンの2剤を使用。ペニシリンアレルギーあるいは一次除菌が失敗した場合の二次除菌としてクラリスロマイシン，メトロニダゾールの2剤を用いる。分2投与とし，治療期間は7日間(～14日間)である。
*カプセルははずして腸溶顆粒として，OD錠は粉砕して投与可。
**腸溶錠の粉砕投与は不可。　(文献4より引用，一部改変)

あるが，効果があったとする症例報告も散見され，治療抵抗性の症例あるいは無治療で経過観察中の症例（血小板数が正常化しない）における治療選択の一つと考えられる。

5 除菌療法（表3）

まず選択される除菌薬剤はプロトンポンプ阻害薬とアモキシシリン，クラリスロマイシンの3剤併用療法である。薬剤アレルギーに注意し，ペニシリンアレルギーがある場合はメトロニダゾールに変更する。投与期間は7日間が原則であるが，小児では14日間投与を推奨する意見もある[4]。副作用として下痢，味覚異常，悪心，発疹などがみられる。除菌成功率は70%前後であり，主な原因はクラリスロマイシン耐性である。特に小児ではクラリスロマイシン耐性株が増加しており，*H. pylori* の培養による抗菌薬感受性試験を行って治療薬剤を決定する方法もある。

6 *H. pylori* 感染診断と除菌治療の保険適用

原則的に18歳以上の成人に適用ありと記載されているが，筆者の知る限りでは小児においても成人と同様の保険診療ができている。

日本ヘリコバクター学会“*H. pylori* 感染の診断と治療のガイドライン”2009

改訂版[6]では，「*H. pylori* 除菌は胃・十二指腸潰瘍の治癒だけではなく，胃癌をはじめとする *H. pylori* 関連疾患の治療や予防，さらには感染経路の抑制に役立つ」とし，*H. pylori* 感染症を除菌治療の適応としている。しかし，現行の保険適用は胃潰瘍，十二指腸潰瘍，胃 MALT リンパ腫，特発性血小板減少性紫斑病，早期胃癌に対する内視鏡術後胃である。除菌前の感染診断については上記5疾患と診断されたもののうち，*H. pylori* 感染が疑われる場合に①迅速ウレアーゼ試験，②鏡検法，③培養法，④抗体測定，⑤尿素呼気試験，⑥抗原測定の検査法で，①～③のうち2項目，④～⑥のうち2項目が算定できる。除菌判定も同じである。*H. pylori* 感染ありと判断された場合には一次除菌治療としてプロトンポンプ阻害薬，アモキシシリン，クラリスロマイシンの3剤併用療法7日間，一次除菌治療に失敗した場合，クラリスロマイシンをメトロニダゾールに変更した3剤併用療法7日間が保険適用となる。鉄欠乏性貧血や慢性胃炎などは現段階では適用外であり，診療に際しては現時点の情報を本人と保護者に十分説明したうえで治療方針を決定することが重要である。

日本では小児の *H. pylori* 除菌治療はまだ十分に普及していないように思える。2005年10月号の小児科学会雑誌に「小児期ヘリコバクター・ピロリ感染症の診断，治療，および管理指針」を掲載している。繰り返す胃・十二指腸潰瘍や原因不明の鉄欠乏性貧血などで苦労している子どもたちや先生方の一助となれば幸いである。

適用外の検査や症例の相談などは筆者（e-mail：okuda@naxnet.or.jp）に連絡いただければ可能な範囲で協力いたします。

（奥田真珠美）

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10

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

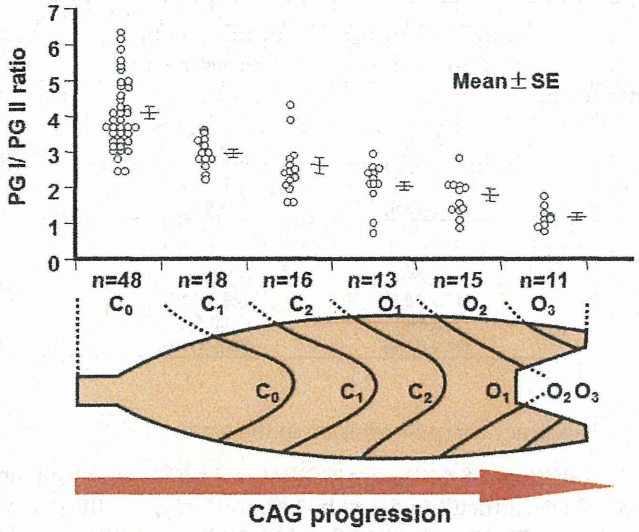

Fig. 1. Relationship between serum pepsinogen (PG)I/PGII ratio and progression of chronic atrophic gastritis (CAG). With atrophic changes in the gastric mucosa progressing from the pyloric glands to more proximally, the serum PGI/II ratio decreases, reflecting an associated loss of PG-producing cells. 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 PGI ≤50 ng/ml and PGI/II ratio ≤3.0 (PG index 2+), and PGI ≤30 ng/ml and PGI/II ratio ≤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	77.3%	68.4%	51.9%
(95%CI)	(69.8-83.8)	(59.1-76.8)	(40.3-63.5)
Pooled specificity	73.2%	69.3%	84.4%
(95%CI)	(72.8-73.6)	(66.6-70.0)	(83.7-85.0)
Our results (Yanaoka et al., 2008a)			
Sensitivity	58.7%	49.2%	27.0%
(95%CI)	(45.6-70.8)	(36.5-62.0)	(16.9-39.9)
Specificity	73.4%	80.5%	92.0%
(95%CI)	(72.1-74.6)	(79.4-81.6%)	(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

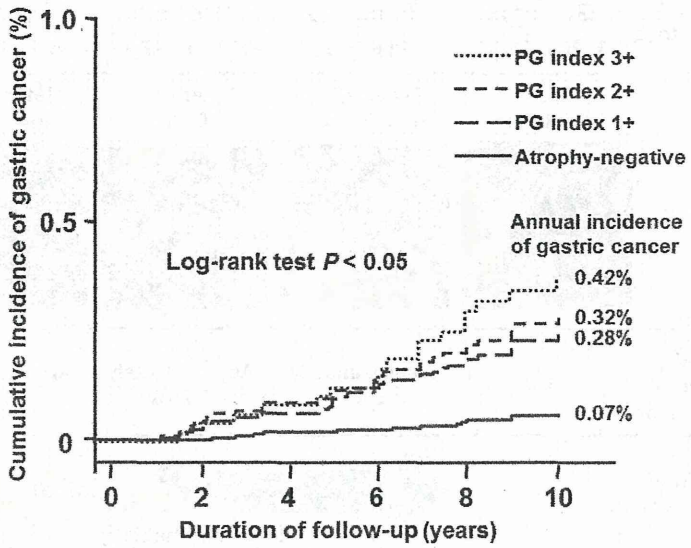

Fig. 2. Kaplan-Meier analysis of gastric cancer development in subjects classified using the criteria of the serum pepsinogen (PG) test. Among middle-aged healthy men, annual incidence of gastric cancer is shown for each population identified using various criteria for the serum PG test. Progression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

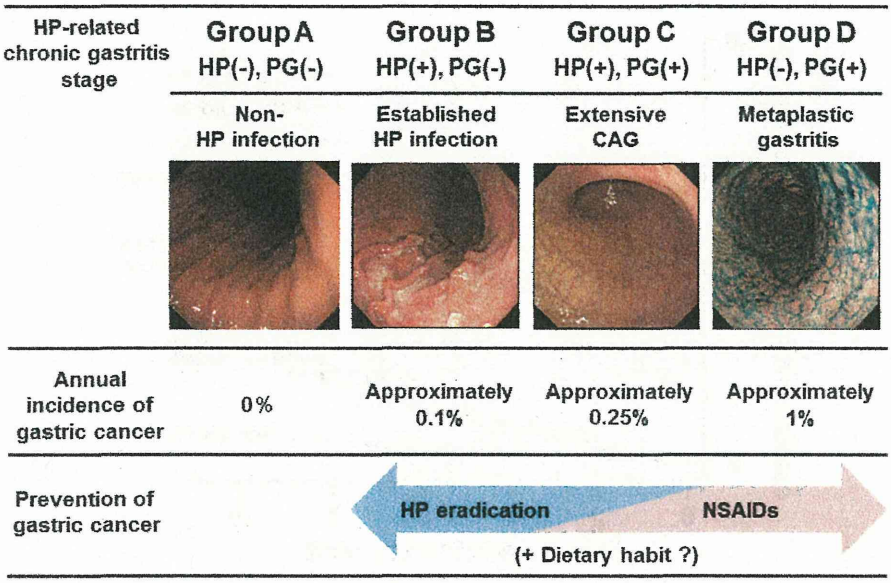

Fig. 3. Gastric cancer risk and prevention of gastric cancer based on *Helicobacter pylori* (HP)-related chronic gastritis stage. This shows the stage classification for HP-related chronic gastritis based on the serum pepsinogen (PG) test and HP antibodies. Among middle-aged healthy men, the annual incidence 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

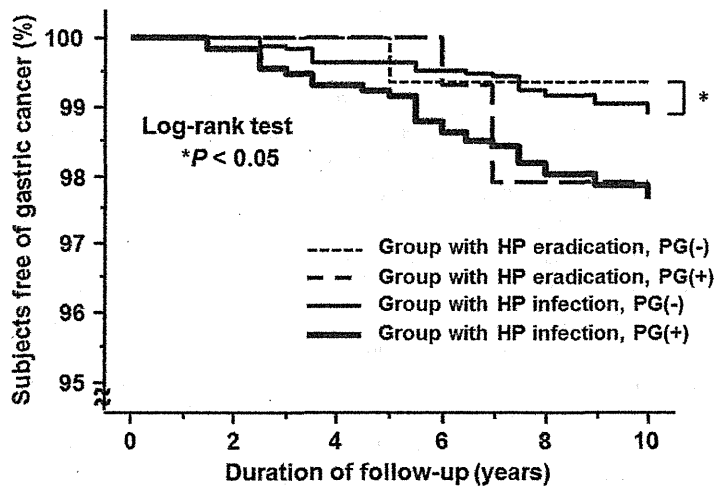

Fig. 4. Kaplan-Meier analysis of the proportion of subjects free of gastric cancer in the serum pepsinogen (PG) test-positive group and the PG test-negative group according to *Helicobacter pylori* (HP) infection status. In the serum PG test-positive group (extensive chronic atrophic gastritis (CAG)), 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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