# Screening Markers for Chronic Atrophic Gastritis in Chiapas, Mexico[1]

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## Abstract

**Intestinal-type gastric adenocarcinomas usually are preceded by chronic atrophic gastritis. Studies of gastric cancer prevention often rely on identification of this condition. In a clinical trial, we sought to determine the best serological screening method for chronic atrophic gastritis and compared our findings to the published literature. Test characteristics of potential screening tests (antibodies to *Helicobacter pylori* or CagA, elevated gastrin, low pepsinogen, increased age) alone or in combination were examined among consecutive subjects enrolled in a study of *H. pylori* and preneoplastic gastric lesions in Chiapas, Mexico; 70% had chronic atrophic gastritis. English-language articles concerning screening for chronic atrophic gastritis were also reviewed. Sensitivity for chronic atrophic gastritis was highest for antibodies to *H. pylori* (92%) or CagA, or gastrin levels >25 ng/l (both 83%). Specificity, however, was low for these tests (18, 41, and 22%, respectively). Pepsinogen levels were highly specific but insensitive markers of chronic atrophic gastritis (for pepsinogen I<25 μg/l, sensitivity was 6% and specificity was 100%; for pepsinogen I:pepsinogen II ratio <2.5, sensitivity was 14% and specificity was 96%). Combinations of markers did not improve test characteristics. Screening test characteristics from the literature varied widely and did not consistently identify a good screening strategy. In this study, CagA antibodies alone had the best combination of test characteristics for chronic atrophic gastritis screening. However, no screening test was both highly sensitive and highly specific for chronic atrophic gastritis.**

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## Introduction

Gastric cancer is the fourteenth leading cause of death in the world and the second leading cause of cancer death (1). Intestinal-type gastric adenocarcinomas, the most common type of gastric cancer (2, 3), are preceded by a series of precancerous lesions, starting with chronic atrophic gastritis, progressing to intestinal metaplasia, dysplasia, and finally becoming cancer; this sequence occurs over several decades (4). Methods that could effectively prevent the development of this disease, either by blocking progression from precancer to cancer or by causing regression of precancer to normal stomach, would represent a significant public health benefit, decreasing the cost both of human suffering and medical expense.

A variety of cancer prevention methods have been hypothesized, including dietary interventions with antioxidants such as vitamin C or A and/or the eradication of *Helicobacter pylori* infection. Epidemiological studies to test interventional methods such as these require the enrollment of people at high risk for cancer into clinical trials. To this end, efficient screening methods to identify people with precancerous conditions would be helpful.

Screening tests should ideally be convenient, virtually free of discomfort or risk, efficient, and economical (5). A commonly used test for the diagnosis of chronic atrophic gastritis, gastric endoscopy with biopsy collection, is invasive and as such has none of these characteristics. A good serological test would be best. A number of studies have examined a variety of serological methods to identify people with precancerous conditions, either as individual tests or as combinations of tests; these include low levels of PGI[4] or a low PGI/II ratio, elevated gastrin levels, and the presence of antibodies to either *H. pylori* or to the CagA protein, a marker of *H. pylori* strain virulence (6–23). Although depressed pepsinogen levels have been considered the best serological marker of gastric preneoplastic conditions to date, these assays are both technically difficult and expensive; additionally, the most appropriate cutoff values remain controversial.

To determine the best screening method for identifying persons with an early gastric condition, chronic atrophic gastritis, we examined a variety of potential screening criteria among consecutive subjects enrolled in an ongoing study of the effect of *H. pylori* eradication on preneoplastic gastric conditions in Chiapas, Mexico. For comparative purposes, these results were then placed within the context of an extensive literature review of similar studies.

## Materials and Methods

**Study Subjects.** The current study was performed as a component of an ongoing clinical trial that examined the effect of *H. pylori* eradication with triple therapy on gastric preneoplastic lesions. Subjects were recruited in Chiapas, Mexico by use

[4] The abbreviations used are: PGI and PGII, pepsinogen I and II.

of radio, printed leaflets, and newspaper advertisements. A questionnaire was administered to each interested person to obtain demographic information; history of cigarette, vitamin supplement, and alcohol use; and history pertinent to study exclusion criteria. Exclusion criteria included the following: age <40 years, current pregnancy, known alcoholism, previous allergic reactions to study medication, history of malignancy, gastrectomy or debilitating medical illness (severe cardiovascular or pulmonary disease, chronic renal failure, or bleeding diatheses), and use of certain medications (digoxin, prednisone, warfarin, and phenytoin). Subjects also had to reside within 25 miles of the Comitan Hospital and have an identifiable address. The study was approved by the Human Subject's Committee at Stanford University, Stanford, CA, at the Colegio de la Frontera Sur, Chiapas, at the Instituto Nacional de Cancerologia (INCAN), Mexico City, and at the Centers for Disease Control and Prevention, Atlanta, GA.

**Serology.** After written informed consent was obtained from each eligible subject, a blood sample was drawn. All samples were tested for antibodies to *H. pylori* using a well-tested ELISA, and to the CagA protein of *H. pylori*, using a highly sensitive and specific assay (antigen courtesy of Oravax, Cambridge, MA) as reported previously (24). Additionally, all samples were tested for fasting serum gastrin concentration via a competitive double antibody commercial RIA (25). Serological criteria for subsequent enrollment into the clinical trial included CagA antibody positivity with gastrin levels ≥25 ng/l. All samples were stored at −70°C.

On completion of the study, samples for this analysis were assayed in a blinded fashion for PGI and PGII levels at the University of Glasgow, Scotland in the laboratory of Professor K. E. L. McColl using a commercial RIA (DiaSorin, Saluggia, Italy).

**Endoscopy.** All eligible subjects identified in the first year of the study underwent upper endoscopy. The stomach mucosa was examined by routine methods. Seven biopsies were systematically collected for histological exam: three from the antrum, three from the body, and one from the cisura angularis.

**Pathology.** The seven biopsies from each subject were embedded in paraffin, cut, and stained with H&E. Histological parameters were evaluated according to the visual-analogue scale of the Revised Sydney Classification (26) and included the presence or absence of the following: *H. pylori*, chronic or acute inflammation, atrophy, goblet cells, brush border, and Paneth cells. A patient was considered to have chronic active gastritis if both acute and chronic inflammation were seen in any of the seven biopsies and to have chronic atrophic gastritis if atrophy was also seen. Suspicious cases where gastritis was observed but where *H. pylori* could not be identified were examined for *H. pylori* with special stains (Warthin-Starry).

All slides were read independently by two general surgical pathologists. All cases in which discrepant diagnoses were found were reviewed by both pathologists together to arrive at a final consensus diagnosis. If necessary, a third pathologist provided additional review. All diagnoses other than the presence or absence of Paneth cells were accompanied by a four-point severity score (none, mild, moderate, or severe).

**Analysis.** The distributions of the screening characteristics and degree of chronic atrophic gastritis as diagnosed by histology were examined in all subjects.

A variety of screening methods to identify chronic atrophic gastritis were examined. Discrete tests considered alone included *H. pylori* antibody positivity, CagA antibody positivity, gastrin ≥25 ng/l and ≥100 ng/l, PGI <25 μg/l and <40 μg/l, and PGI/II <2.5 and <4. We also considered age ≥60 years, given that age is universally available and that older people are at higher risk of chronic atrophic gastritis (27). Because our clinical trial used screening criteria of CagA antibody positivity and elevated gastrin, we also evaluated combinations of tests. Combinations of tests included the following: *H. pylori* or CagA antibody positivity and gastrin ≥25 ng/l; *H. pylori* or CagA antibody positivity and age ≥60 years; *H. pylori* or CagA antibody positivity and PGI <25 μg/l or <40 μg/l; gastrin ≥ 25 ng/l and PGI <25 μg/l or <40 μg/l; *H. pylori* or CagA antibody positivity and PGI/II <2.5 or <4. Subjects with and without chronic atrophic gastritis based on histology were categorized as meeting or not meeting each screening criterion. Sensitivity, specificity, and positive and negative predictive values for chronic atrophic gastritis were calculated for each screening method; 95% confidence intervals were established for each parameter (28). Receiver-operator characteristic curves were calculated for all continuous variables (age, pepsinogen and gastrin levels) alone and in combination with CagA antibody positivity.

Because predictive values are affected by the background prevalence of the condition of interest, we examined how positive predictive values for several tests varied with the prevalence of chronic atrophic gastritis.

The diagnosis of chronic atrophic gastritis is sometimes questionable when the degree is mild, particularly in the context of active inflammation (26). To examine the effect of this potential misclassification, we recalculated test characteristics after reclassifying subjects in two ways. First, instead of comparing people with no chronic atrophic gastritis with people with any (*i.e.*, mild, moderate, or severe) chronic atrophic gastritis, we compared persons with no or mild chronic atrophic gastritis with those with either moderate or severe chronic atrophic gastritis. This analysis would identify test characteristics for either moderate or severe chronic atrophic gastritis. Second, we compared people with no chronic atrophic gastritis with only those with severe chronic atrophic gastritis, omitting the intermediate categories. Although this second approach decreased sample size, we felt that it minimized the potential misclassification of mild chronic atrophic gastritis.

## Results

A total of 205 consecutive subjects was enrolled from November 1996 to October 1997; of these, 178 (87%) and 155 (76%) had antibodies to *H. pylori* and CagA, respectively. Of the 205 subjects, 124 (61%) were women; the mean age was 52.3 years (SD, ± 9.7 years). The gastrin level was missing for one subject; PGI and PGII levels were available for 149 (73%) and 148 (72%) subjects, respectively. The median levels for gastrin, PGI, and the PGI/II ratio were 35 ng/l, 95 μg/l, and 15, respectively (25–75% ranges, 26–52 ng/l, 59–122 μg/l, and 9–22, respectively). A total of 182 (89%) had histological evidence of *H. pylori* infection, and 144 (70%) subjects had histological evidence of chronic atrophic gastritis. Among these 144 people with chronic atrophic gastritis, the diagnosis was mild, moderate, and severe in 57 (40%), 74 (51%), and 13 (9%), respectively.

Evaluation of selected screening methods is presented in Table 1. Among serological tests alone, the presence of antibodies to *H. pylori* had the highest sensitivity (92%) but poor specificity (18%). The presence of antibodies to CagA or gastrin levels ≥25 ng/l had similar sensitivities for chronic atrophic gastritis (both 83%) but different low specificities (41 and 22%, respectively). PGI <25 μg/l or PGI/II <2.5 had

*Table 1* Test characteristics (with 95% confidence intervals) of the different screening methods for chronic atrophic gastritis[a]

| | Sensitivity (%) | Specificity (%) | Predictive value positive (%) | Predictive value negative (%) |
|---|---|---|---|---|
| *H. pylori* antibodies | 91.7 (86.8–94.9) | 18.0 (13.2–24.1) | 72.5 (65.8–78.4) | 44.4 (40.9–54.9) |
| CagA antibodies | 82.6 (76.6–87.4) | 41.0 (34.2–48.1) | 76.8 (70.3–82.3) | 50.0 (43.0–57.0) |
| Gastrin ≥25 ng/l[b] | 82.6 (76.6–87.4) | 21.7 (16.4–28.1) | 71.7 (64.9–77.7) | 34.2 (27.8–41.2) |
| PGI <25 μg/l[b] | 5.8 (2.8–11.2) | 100 (96.9–100) | 100 (96.9–100) | 32.2 (24.9–40.4) |
| PGI/PGII <2.5[b] | 13.7 (8.8–20.6) | 95.7 (90.6–98.2) | 87.5 (80.8–92.2) | 33.3 (25.9–41.6) |
| Age ≥60 years | 25.7 (20.0–32.3) | 88.5 (83.2–92.4) | 84.1 (78.2–88.7) | 33.5 (27.2–40.5) |
| CagA antibodies + gastrin ≥25 ng/l | 69.4 (62.6–75.6) | 46.7 (39.7–53.8) | 75.8 (69.2–81.4) | 38.9 (32.2–46.0) |
| CagA antibodies + PGI <25 μg/l | 4.9 (2.2–10.0) | 100 (96.9–100) | 100 (96.9–100) | 31.9 (24.7–40.2) |
| CagA antibodies + PGI/PGII <2.5 | 11.8 (7.3–18.3) | 95.7 (90.6–98.2) | 85.7 (78.8–90.7) | 32.8 (25.5–41.1) |
| PGI <25 μg/l + gastrin ≥25 ng/l | 5.8 (2.8–11.2) | 100 (96.9–100) | 100 (96.9–100) | 32.2 (24.9–40.4) |
| PGI/PGII <2.5 + gastrin ≥25 ng/l | 11.8 (7.3–18.3) | 95.7 (90.6–98.2) | 85.7 (78.2–90.3) | 32.8 (25.5–41.1) |
| CagA antibodies + Age ≥60 years | 20.1 (15.0–26.4) | 96.7 (93.0–98.6) | 93.6 (89.0–96.4) | 33.9 (27.6–40.9) |

[a] None *vs.* mild/moderate/severe.
[b] One person was not tested for gastrin, 56 were not tested for PGI, and 57 were not tested for PGII levels.

extremely high specificities (96–100%) but poor sensitivities (6–14%). Age ≥60 years was an insensitive but fairly specific marker of chronic atrophic gastritis (sensitivity, 26%; specificity, 89%).

The addition of gastrin ≥25 ng/l to CagA antibodies provided no additional increase in sensitivity and specificity compared with CagA antibodies alone. The addition of pepsinogens to CagA antibodies or gastrin ≥25 ng/l improved specificities and positive predictive values, but dramatically decreased sensitivities. Adding age ≥60 years to CagA antibodies improved specificity and decreased sensitivity. Parallel results were found for the same combinations with *H. pylori* antibodies instead of CagA antibodies: although specificity increased, sensitivity decreased considerably (data not shown). Receiver-operator characteristic curves for the continuous variables of age, gastrin, and pepsinogens showed that these variables were uniformly poor screening tests for chronic atrophic gastritis (data not shown).

All tests alone or in combination had poor negative predictive values, with that for CagA antibodies alone being the best (50%). We examined the positive predictive values of several tests across a hypothetical increasing population prevalence of chronic atrophic gastritis. All tests other than PGI had very low positive predictive power at low population prevalences of chronic atrophic gastritis. The predictive power of PGI levels <25 μg/l was 100% across all prevalences of chronic atrophic gastritis, in part because of the very small sample size of persons with low PGI (4%). Other tests required a population prevalence of chronic atrophic gastritis of between 55 and 80% before reaching a positive predictive value of at least 80% (data not shown).

Considering mild chronic atrophic gastritis as no chronic atrophic gastritis decreased the overall prevalence of chronic atrophic gastritis in this sample to 42.4%. The sensitivity and specificity for all screening tests were minimally decreased, whereas the positive predictive value substantially decreased and the negative predictive value increased (data not shown). Similar results were found when only subjects with either no or severe chronic atrophic gastritis were compared, *i.e.*, low positive predictive values and very high negative predictive values (data not shown).

## Discussion

In a consecutive sample of healthy volunteers undergoing serological testing and gastric endoscopy in Chiapas, Mexico, we examined a wide variety of screening criteria both alone and together to determine which best identified persons with chronic atrophic gastritis. No test was both highly sensitive and highly specific. The highest sensitivities were found for the presence of antibodies to *H. pylori* or CagA and elevated gastrin levels, whereas the highest specificities were found for low pepsinogen levels (either alone or in combination) and age >60 years. The presence of CagA antibodies alone had the best combination of sensitivity and specificity (83 and 41%, respectively). Adding further tests such as elevated gastrin (≥25 ng/l) or increased age (≥60 years) to the presence of CagA antibodies did not improve sensitivities, which declined considerably. In the present clinical trial, our use of eligibility criteria based on elevated gastrin in addition to antibodies to CagA led us to discard an additional 11% of volunteers from consideration, of whom 83% had chronic atrophic gastritis. For future large-scale trials of gastric cancer prevention in the presence of preneoplastic conditions, determining optimal screening criteria should be an important concern given the financial expense and time that often is incurred to identify eligible subjects.

The positive predictive values for all screening tests were high; this finding is attributable solely to the very high prevalence of chronic atrophic gastritis in our population. The diagnosis of mild chronic atrophic gastritis is controversial, particularly in the context of active inflammation and a total of 28% of our sample was diagnosed with this condition. To examine this potential misclassification, we grouped cases of mild chronic atrophic gastritis as none, decreasing the overall prevalence; the positive predictive values fell accordingly. Despite this reclassification, however, the prevalence of chronic atrophic gastritis still exceeded 40% in our sample. Such a high background prevalence of moderate or severe chronic atrophic gastritis may be partially explained by the nearly universal infection with *H. pylori* in both this sample and this region (29, 30). *H. pylori* strains that express the CagA protein are more strongly associated with gastric carcinoma than CagA-negative strains, possibly by causing an increase in the occurrence of atrophic gastritis (31).

Sensitivity and specificity are properties of individual screening tests, and unlike predictive power, which is affected by background disease prevalence, they should not vary greatly across populations. In the case of chronic atrophic gastritis, however, tests appear to be quite variable. Generally, gastrin levels are known to be higher and pepsinogen levels lower in subjects with atrophic gastritis compared with normal controls. These markers have been shown to discriminate between affected and unaffected people in some studies (6, 12, 16, 22, 32)

*Table 2* Literature review of the sensitivity and specificity of various screening tests for chronic atrophic gastritis, classified by diagnostic method

| Reference | Subjects (location) | Screening test | Outcome | Outcome prevalence (%) | Diagnostic method[a] | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|---|
| Varis *et al.* (20) | 159 relatives of patients with pernicious (Finland) | PGI <20 μg/l | Atrophy | 13.4 | NS[b] | 91.3 | 97.3 |
| | | Gastrin >100 ng/l | | | | 82.6 | 97.3 |
| | | PGI <20 μg/l + gastrin >100 ng/l | | | | 82.6 | 100 |
| Samloff *et al.* | 170 relatives of patients with pernicious (Finland) | PGI <62 μg/l + PGI/II <4.3 | AG (0)[c] | 13.5 | NS | 91.3 | 98.6 |
| | | PGI <62 μg/l + PGI/II <4.3 | AG | 23.5 | | 57.5 | 92.3 |
| Kekki *et al.* (10) | 276 relatives of gastric cancer patients | PGI <25 μg/l | AG (1) | 2.7 | NS | 89.5 | 93.9 |
| | | PGI <30 μg/l | | | | 89.5 | 91.5 |
| | 424 matched controls | Gastrin >200 ng/l | | | | 31.6 | 95.9 |
| | 73 relatives of patients with pernicious anemia (Finland) | Gastrin >100 ng/l | | | | 57.9 | 90.2 |
| Guarner *et al.* (29) | 217 symptomatic patients | *H. pylori* (serology) | Atrophy | 77.4[d] | NS | 93.4 | 50 |
| | 28 asymptomatic controls (Mexico) | *H. pylori* (pathology) | | 72.7[e] | | 92.3 | 21.1 |
| Halissey *et al.* (8) | 432 dyspepsia patients | PGI <20 μg/l | AG, IM, or polyp | 16.1 | NS | 6 | 98.6 |
| | 26 asymptomatic controls (United Kingdom) | PGI <30 μg/l | | | | 11.9 | 96 |
| Inoue *et al.* (7) | 200 endoscopy patients (Japan) | PGI ≤30 μg/l + PGI/II <2 | Atrophy | 58.5 | NS | 18.8 | 100 |
| | | PGI ≤70 μg/l + PGI/II ≤3 | | | | 65 | 92.8 |
| | | PGI ≤40 μg/l + PGI/II ≤2.5 | | | | 82.1 | 74.7 |
| | | *H. pylori* (serology) | | | | 85.5 | 37.3 |
| Faisal *et al.* (34) | 125 healthy adults ages ≥65 years (United States) | *H. pylori* (serology) | AG | 10.4 | PGI/PGII <2.9 + PGI <20 μg/l | 38.5 | 51.1 |
| Borch *et al.* (6) | 179 patients with AG | PGI <71.6 μg/l | Atrophy | 78.2 | Whitehead | 96.6 | 86 |
| | 29 gastric cancer patients | PGI/II <5.5 | Atrophy | | | 99.4 | 94 |
| | 15 gastrectrectomy patients | PGI <71.6 μg/l | AG (0) | 74.6 | | 100 | 86 |
| | 50 normal controls (Sweden) | PGI/II <5.5 | AG (0) | | | 99.3 | 94 |
| Sitas *et al.* (19) | 87 endoscopy patients (United Kingdom) | PGI/II <1.5 | AG (2) | 25.3 | Whitehead | 26.7 | 89.1 |
| | | *H. pylori* (serology) | | | | 86.7 | 78.3 |
| | | *H. pylori* + PCI/PCII <1.5 | | | | 26.7 | 95.7 |
| Zhang *et al.* (23) | 2646 healthy adults, ages 35–64 years (China) | PGI/II <5 | Atrophy | 8.2 | Chinese Assoc. of Gastric Cancer | 19.2 | 72.1 |
| | | *H. pylori* (serology) | | | | 87.5 | 29.7 |
| Hu *et al.* (35) | 161 *H. pylori*-positive non-ulcer dyspepsia patients (China) | Age >40 years | Atrophy | 59.6 | Sydney | 75 | 72.3 |
| Kuipers *et al.* (13) | 58 *H. pylori*-positive patients with follow-up (the Neterlands) | CagA (overall; serology) | Atrophy | 44.8[f] | Sydney | 57.7 | 71.9 |
| | | CagA (at baseline) | | 24.1[g] | | 57.1 | 63.6 |
| | | CagA (at follow-up) | | 31.8[h] | | 42.9 | 66.7 |
| Asaka *et al.* (36) | 85 healthy adults (Japan) | *H. pylori* (serology) | Atrophy | 52.9 | Sydney | 96 | 45 |
| Knight *et al.* (11) | 6 workers with PGI <25 μg/l | PGI <25 μg/l | Atrophy | 17.6 | Sydney | 44.4 | 97.6 |
| | 19 workers with PGI >150 μg/l | *H. pylori* (serology) | | | | 100 | 59.5 |
| | 34 matched controls | PGI <80 μg/l + *H. pylori* | | | | 88.9 | 92.3 |
| | (United Kingdom) | PGI <80 μg/l + *H. pylori* + PGI/II <2.5 | | | | 77.8 | 100 |
| Pilotto *et al.* (15) | 71 endoscopy patients age ≥60 years (Italy) | CagA (by PCR) | Atrophy | 26.8 | Sydney | 78.9 | 57.7 |

[a] Method used to assess atrophy.
[b] NS, not stated; AG, atrophic gastritis; IM, intestinal metaplasia.
[c] Atrophic gastritis: 0, severe; 1, severe diffuse; 2, moderate chronic.
[d] Analysis with serology.
[e] Analysis with pathology.
[f–h] Prevalence: overall; at baseline; at follow-up.

but not in others (8, 33). A number of investigations have determined the sensitivity and specificity of these and other screening tests for a range of cutoff values, either directly or by providing data permitting their calculation (Table 2 and Refs. 6, 8, 10, 11, 13, 15, 17, 19, 20, 23, 29, 34–36). For each screening test, variation in both sensitivity and specificity is remarkably wide.

Although this enormous variation across studies can be

attributed in part to differences in study design, underlying population characteristics (such as country of origin or patient selection criteria), and very different cutoff values, it may be explained largely by the lack of a standardized method for diagnosing atrophic gastritis. Studies have used different diagnostic methods: some studies considered only severe atrophy, whereas others considered any atrophy; overall, the prevalence of this condition ranged from 3 to 78%. Indeed, even among collaborating pathologists, rates of agreement regarding the diagnosis of chronic atrophic gastritis have been notoriously poor (37). The Sydney classification and its subsequent 1990 revision were developed as a standard method for evaluating gastric lesions, and include a visual analogue scale for diagnosing and grading atrophy (26). Standardization permits direct comparison across studies. Five recent investigations examined a variety of screening tests for chronic atrophic gastritis diagnosed using the Sydney classification (11, 13, 15, 29, 36). Unfortunately, however, few examined the same test, and no two considered either the same location or same type of subjects [who ranged from healthy adults (36) to symptomatic patients undergoing endoscopy (15)]. Probably because of these facts, the range of prevalence of atrophy remained wide. From this small number of studies in disparate populations, it again appears that no test has particularly good characteristics, although overall, measures of *H. pylori* infection provide high sensitivity and measures of pepsinogen high specificity. Results from our study confirm these trends; confirmatory investigations directly comparing the same tests in similar populations would be particularly helpful for setting this question to rest.

Our study confirms the excellent specificity of low PGI levels found in the study by Knight *et al.* (11), but suggests that sensitivity may be even poorer than reported previously. Using our data to repeat the combinations of pepsinogens and *H. pylori* from the study by Knight *et al.*, we identified lower sensitivities (34.0 and 9.8% *versus* 88.9 and 77.8%; data not shown). These results illustrate the difference between tests that may have clinical usefulness, and those that may be important for large-scale population screening programs. PGI levels may confirm the absence of chronic atrophic gastritis in a particular patient, but they are less useful in identifying persons at risk of this condition at the population level. It is possible that some degradation of pepsinogens occurred during the storage of our samples, leading to an increased proportion of subjects with pepsinogen levels $<25$ $\mu$g/l. In this situation, if we corrected for this misclassification, the specificity would remain excellent but the sensitivity would further decrease.

A common limitation to studies of screening tests is the use of a very select group of patients, often with clinical disease. In our study, we enrolled all consecutive healthy volunteers over a 12-month period who agreed to donate blood; those who chose to undergo the subsequent endoscopy were demographically and serologically similar to the very few who did not (data not shown). Chiapas is an impoverished mountainous region of Mexico where both rates of preneoplastic conditions and gastric cancer and concern for this disease are very high (30). Because of this, we believe that our screening results are valid for the population of Chiapas. Additionally, the use of healthy volunteers may partially explain the rate of severe atrophy seen in this study (6%), which is low particularly compared with the initial investigations of screening pepsinogens. These studies were performed among relatives of Finnish patients with pernicious anemia, where the prevalence of severe atrophy was 13.5% (17, 20). This comparison shows the importance of having screening tests that can identify intermediate stages of disease, such as moderate atrophy.

To minimize interpathologist disagreement with respect to the diagnosis of chronic atrophic gastritis, we examined seven biopsies and required an independent review of each biopsy by the two pathologists with a final consensus diagnosis for each subject. To take into consideration the possible overdiagnosis of chronic atrophic gastritis (pathologists may have diagnosed mild atrophy when in fact there was none), we repeated our analyses, categorizing chronic atrophic gastritis as either none/mild or moderate/severe. In this situation, the prevalence of chronic atrophic gastritis in our sample decreased substantially. As expected, whereas the positive predictive value decreased, the sensitivity and specificity of the screening tests remained virtually unchanged.

Ideally, a screening test has both high sensitivity and high specificity. More often in reality, however, screening tests are either highly sensitive or highly specific. For the purpose of recruitment into population-based epidemiological studies of cancer prevention, screening tests should primarily be sensitive, with a goal of maximum enrollment of at-risk people. In this situation, specificity becomes more important as the individual's cost of falsely being labeled positive for preneoplasia increases. For people with chronic atrophic gastritis, the long-term prognosis is not clear. Thus, the effects of including in a cancer prevention trial a person incorrectly labeled as having chronic atrophic gastritis will be limited to, for the individual, the proposed therapy, and for the study, an uninformative individual. The benefit to including in a prevention trial as many people with true chronic atrophic gastritis as possible is that sufficient sample size can be obtained. Our experience in Chiapas suggests that in populations with a high prevalence of chronic atrophic gastritis, serological screening with CagA alone is the most effective test for identifying eligible subjects.

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