Serum Pepsinogen Levels, *Helicobacter pylori* CagA Status, and Cytokine Gene Polymorphisms Associated with Gastric Premalignant Lesions in Costa Rica

Sergio A. Con,1,4,5 Reinaldo Con-Wong,1 Gil R. Con-Chin,1 Vicky G. Con-Chin,1 Hiroaki Takeuchi,5 Ana L. Valerı́n,1 Guillermo Echandi,2 Fernando Mena,3 Fernando Breñes,3 Nobufumi Yasuda,6 Keiı́ji Araki,4 and Tetsuro Sugı́ra5
1Centro Digestivo Doctores Con-Mediplaza; 2Laboratorio Clı́nico Echandi-Mediplaza; 3Laboratorio de Patologı́a-Mediplaza, Pavas, San José, Costa Rica; and Departments of *Tumor Surgery, Clinical Laboratory Medicine, and Public Health,* Kochi Medical School, Kochi University, Nankoku-city, Kochi, Japan

Abstract

The detection of gastric premalignant lesions, atrophic gastritis, corpus atrophic gastritis, and intestinal metaplasia, using several potential markers was examined in Costa Rica. Depending on the lesion investigated, from a total of 223 dyspeptic patients, 58 (26.0%), 31 (13.9%), or 23 (10.3%) were histologically diagnosed with atrophic gastritis, corpus atrophic gastritis, or intestinal metaplasia, respectively. Sera were used for the measurement of pepsinogen (PG) and *Helicobacter pylori* CagA antibody (CagA-ab) levels by ELISA, and human genomic DNAs were used for the genotyping of interleukin (IL)-1 (−511 and +3954), IL-10 (−1082 and −392), and IL-1RN intron 2 by PCR and RFLP. Multivariate analysis was done adjusting for sex, age, and *H. pylori* seropositivity. Low PG levels (L-PG; PG I ≤70 µg/L + PG I/II ≤3), very low PG levels (VL-PG; PG I ≤30 µg/L + PG I/II ≤2), and CagA-ab were individually associated with all premalignant lesions whereas IL-1β +3954T-carrier and IL-1RN homozygous 2 allele were associated with intestinal metaplasia. VL-PG, for corpus atrophic gastritis detection, was the single marker with the highest combination of test characteristics, sensitivity (77.4%), specificity (80.7%), positive predictive value (93.3%), negative predictive value (95.7%), and seropositivity rate (27.4%), expected to improve after periodic measurements. Combined examinations of VL-PG and CagA-ab improved the specificity (92.7%) and positive predictive value (62.2%), with similar sensitivity (74.2%) and negative predictive value (95.7%). In conclusion, corpus atrophic gastritis detection with periodic measurements of serum PG, alone or in combination with CagA-ab status, to identify high gastric cancer risk, seems to be the method best suited for mass screening in Costa Rica. (Cancer Epidemiol Biomarkers Prev 2007;16(12):2631–6)

Introduction

Gastric cancer is the second leading cause of cancer-related death worldwide (1). Costa Rica is one of the countries with the highest incidence and mortality rates in the world (2). In fact, during 1983 to 1997, among 30 listed countries including Japan and Chile, Costa Rica had the highest age-adjusted death rate for gastric cancer for males and females (3). For this reason, much effort has to be directed toward the detection of early gastric cancer in this country.

The cause of gastric cancer is thought to be multifactorial—a result of an interplay of environmental factors, bacterial pathogenesis, and host genetic factors including male predominance (4) and blood type A (5, 6). Atrophic gastritis and intestinal metaplasia, which are well-documented risk factors for gastric cancer (7, 8), are later stages in the model of histologic progression in gastric carcinogenesis (9). Atrophic gastritis is thought to develop primarily in the antrum, and corpus atrophic gastritis, referred to as the detection of the atrophic process in the gastric corpus, often results in a more severe degree of glandular atrophy (8, 9) and hence has been more closely associated with the risk of developing gastric cancer than atrophic gastritis (7, 10).

For the direct diagnosis of atrophic gastritis and intestinal metaplasia, histologic observation from biopsy specimens is the gold standard method. However, there are other methods that are noninvasive and low in cost that seem more suited for mass screening detection of these lesions. In fact, the serologic markers, serum pepsinogen (PG) levels and *Helicobacter pylori* CagA antibodies (CagA-ab) status, have both been evaluated as screening criteria for the detection of atrophic gastritis in several studies (11-20). Other markers such as human genetic polymorphisms within the cytokine genes *interleukin* (IL)-1 and IL-10 have been associated with an increased risk for gastric cancer, probably due to the induction of a hypochlorhydric and
atrophic response to \textit{H. pylori} infection, with atrophic and metaplastic changes in the gastric mucosa (21-23). Furthermore, the combination of bacterial pathogenicity (\textit{cagA}+ and \textit{vacA s1}) and host genetic factors (IL-1 gene polymorphisms) has been associated with severe histologic changes in the gastric mucosa (24).

Due to the marked geographic variations in the distribution of both \textit{H. pylori} strain genotyping and the host genetic cytokine polymorphisms, it remains to be elucidated whether any of these factors, alone or combined, could effectively detect gastric premalignant lesions in the Costa Rican population.

The aim of this study was to evaluate the influence of several potential markers, including serum PG levels, \textit{CagA}-ab status, and cytokine gene polymorphisms, on the development of gastric premalignant lesions in a Costa Rican population to determine which factor was the best suited method for mass screening detection of subjects at high risk for gastric cancer in this country.

**Materials and Methods**

**Recruitment of Patients.** A total of 223 Costa Rican patients were consecutively examined at a digestive center in Mediplaza, San Jose, Costa Rica between January and October 2005. The study was approved by the Ethics Committee of the institution and written informed consent was obtained from each patient. Background data were collected on age, gender, symptoms, and medication. Patients with \textit{H. pylori} eradication, attempted eradication therapy, or previous gastric surgery were not included in this study. Likewise, patients who had received proton pump inhibitors, antibiotics, nonsteroidal anti-inflammatory drugs, or any drug that could alter the state of the gastric mucosa ≤3 months before the endoscopic examination were not enrolled in this study.

**Endoscopic Evaluation.** Endoscopy was done with Olympus Evis Excera 160 videendoscopes (Olympus America, Inc.). Five biopsies were collected from each patient for histologic examination: two from the antrum, two from the corpus, and one from the cissura angularis. Another antral biopsy was obtained for the detection of \textit{H. pylori} by a commercially available rapid urease test (Laboratorio San Jose).

**Histologic Evaluation.** The five biopsy samples from each patient were conventionally fixed in 10% of formaldehyde and embedded in paraffin. Serial sections (3–4 μm) were stained with H&E for histologic observation. Each biopsy specimen was evaluated independently by two experienced pathologists blinded to the endoscopic and serologic examinations. All discrepant diagnoses found were reexamined by both pathologists together to reach a final consensus diagnosis. All five biopsies were examined for the presence of \textit{H. pylori}, neutrophilic infiltration, atrophic gastritis, and intestinal metaplasia and were scored into four grades (0, none; 1, mild; 2, moderate; and 3, marked) for both the antrum and the body of the stomach according to the updated Sydney System of classification and grading of gastritis (25). Atrophic gastritis was defined as the loss of gastric glands and its replacement with fibrosis or metaplastic epithelium. Atrophic gastritis was histologically diagnosed when glandular atrophy was visualized in any part of the stomach whereas corpus atrophic gastritis was diagnosed when the atrophy was visualized in the body of the stomach. Intestinal metaplasia was histologically diagnosed when the presence of foci at least three neighboring gastric pits containing two or more goblet cells (in each pit) were visualized in any part of the stomach.

**Serologic Analysis.** Peripheral blood was collected from each patient and sera obtained by centrifugation were stored at –20°C until analysis. The titers of \textit{H. pylori} and \textit{H. pylori} CagA antibodies were measured with commercial ELISA (Eiken Chemical Co., Ltd.) and CagA IgG EIA Well (Radim), respectively, according to the instructions of the manufacturer.

Serum PG I and II levels were measured using E Plate Pepsinogen I and II (Eiken Chemical Co., Ltd.) using cutoff levels PG I ≤70 μg/L + PG I/II ratio ≤3 as low PG levels (L-PG) and PG I ≤30 μg/L + PG I/II ratio ≤2 as very low PG levels (VL-PG) according to the instructions of the manufacturer.

**Determination of \textit{H. pylori} Infection.** \textit{H. pylori} infection was determined by serum antibodies to \textit{H. pylori}, rapid urease test, or histologic examination in biopsy specimens obtained from the antrum, cissura angularis, and body of the stomach. Patients were considered to be infected with the bacterium if the serum antibodies to \textit{H. pylori} were found, the biopsy specimen was positive for the rapid urease test, or the bacterium was observed in any of the H&E-stained sections.

**Isolation of Human DNA and Genotyping of Cytokine Polymorphisms.** Human genomic DNA was extracted from blood samples with a DNA extraction kit (QIAGen DNA mini kit, Qiagen K.K.) according to the instructions of the manufacturer. Genotyping of IL-1\(\beta\) –511, IL-1\(\beta\) +3954, IL-10 –1082, and IL-10 –592 was done by PCR and RFLP, as previously described (26, 27). PCR products were sized by electrophoresis on a 3% agarose gel stained with ethidium bromide (5%). The IL-1RN intron 2 variable number of tandem repeat polymorphism was examined by PCR and electrophoresis on 2% agarose gels. The alleles were classified conventionally according to El-Omar et al. (21) as follows: allele 1, four repeats; allele 2, two repeats; allele 3, five repeats; allele 4, three repeats; and allele 5, six repeats. Because alleles 3, 4, and 5 were very rare, the alleles were classified into short (allele 2: *2*) and long (alleles 1, 3, 4, and 5: L) alleles for statistical analysis as previously described (23).

**Statistical Analysis.** Sensitivity, specificity, positive predictive value, negative predictive value, odds ratios (OR), and 95% confidence intervals (95% CI) were calculated using Epidat (version 3.1) statistical software. \(\chi^2\) test, Fisher’s exact probability test, and multiple logistic regression models adjusting for sex, age, and \textit{H. pylori} seropositivity were done using SPSS 13.0 J (SPSS Japan, Inc.; 2005), with \(P < 0.05\) being considered statistically significant.

**Results**

**Characteristics of Patients.** A total of 223 patients [94 men and 129 women; mean age, 51.17 ± 12.8 (SD) years] were enrolled in this study. Depending on the
premalignant lesion studied, atrophic gastritis, corpus atrophic gastritis, and intestinal metaplasia were histologically confirmed in 58 (26.0%), 31 (13.9%), and 23 (10.3%) patients, respectively (Table 1). The mean age was significantly higher for atrophic gastritis-, corpus atrophic gastritis-, and intestinal metaplasia-positive patients than for atrophic gastritis- and corpus atrophic gastritis-negative patients, whereas the prevalence of *H. pylori* was significantly higher in atrophic gastritis- and corpus atrophic gastritis-positive patients than in atrophic gastritis- and corpus atrophic gastritis-negative patients. Gender distribution showed no significant difference in any of the groups evaluated. PG I, PG II, *H. pylori* infection,

### Table 1. Characteristics of Costa Rican dyspeptic patients

<table>
<thead>
<tr>
<th>Atrophic gastritis</th>
<th>Corpus atrophic gastritis</th>
<th>Intestinal metaplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td><strong>Sex (male/female)</strong></td>
<td><strong>Mean age ± SD (y)</strong></td>
</tr>
<tr>
<td>58</td>
<td>23/35</td>
<td>49 ± 12</td>
</tr>
<tr>
<td>165</td>
<td>71/94</td>
<td>59 ± 11</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td><strong>Pos Neg</strong></td>
<td><strong>Pos Neg</strong></td>
</tr>
<tr>
<td>0.65</td>
<td>0.001</td>
<td>0.029</td>
</tr>
</tbody>
</table>

**Abbreviations:** Pos, positive; Neg, negative; *HP, H. pylori*.

### Table 2. Adjusted ORs with 95% CIs for several potential markers according to atrophic gastritis, corpus atrophic gastritis, and intestinal metaplasia in Costa Rican dyspeptic patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>Atrophic gastritis</th>
<th>Corpus atrophic gastritis</th>
<th>Intestinal metaplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pos/Neg OR (95% CI)</td>
<td>Pos/Neg OR (95% CI)</td>
<td>Pos/Neg OR (95% CI)</td>
</tr>
</tbody>
</table>

**NOTE:** T carrier, T/T + T/C; A carrier, A/A + G/A or C/A; L, alleles 1, 3, 4 and 5; *2 carrier, *2/*2 + *2/L. HP-neg, *H. pylori* negative. ORs are adjusted for sex, age, and *H. pylori* seropositivity.

*With cutoff levels PG I ≤70 μg/L + PG I/II ≤3.

†P < 0.001, vs controls.

‡With cutoff levels PG I ≤30 μg/L + PG I/II ≤2.

§P < 0.01, vs controls.

∥P < 0.05, vs controls.
The presence of IL-1 associated with elevated risk of atrophic gastritis, corpus atrophic gastritis and intestinal metaplasia in Costa Rican dyspeptic patients. Genotyping of the cytokine polymorphisms was successfully done in 207 (92.8%) patients.

**Single Markers and Gastric Premalignant Lesions.** The presence of L-PG, VL-PG, and CagA-ab was associated with elevated risk of atrophic gastritis, corpus atrophic gastritis, and intestinal metaplasia whereas the presence of IL-1+3954T-carrier (IL+3954T) and IL-1 receptor antagonist homozygous 2 allele (IL*2/2) was only associated with intestinal metaplasia (Table 2).

Other factors evaluated, including IL-1α−511 and IL-10 polymorphisms, were not associated with any gastric premalignant lesion.

**Test Characteristics of Single Markers Associated with Gastric Premalignant Lesions.** The marker with the highest sensitivity rate, for detection of atrophic gastritis, corpus atrophic gastritis, and intestinal metaplasia, was CagA-ab (82.8%, 90.3%, and 95.7%, respectively). However, this marker had a very low specificity rate (51.5%, 47.9%, and 47.0%, respectively; Table 3). On the contrary, the detection of the serum PG as well as the cytokine polymorphism markers had a high specificity rate. VL-PG, for detection of corpus atrophic gastritis, was the marker with the best combination of sensitivity and specificity rates (77.4% and 80.7%, respectively).

**Combined Markers and Gastric Premalignant Lesions.** To investigate the influence of combined factors on the development of precancerous lesions, we used the markers that were found statistically associated with the gastric premalignant lesions evaluated in this study. Because L-PG, VL-PG, and CagA-ab were significantly associated with atrophic gastritis, each of them was defined as a high-risk factor for this lesion. Likewise, each of the same three markers was defined as a high-risk factor for corpus atrophic gastritis. For detection of intestinal metaplasia, the markers L-PG, VL-PG, CagA-ab, IL-3954T, and IL*2/2 were considered as high-risk factors for this lesion.

The combination of VL-PG and CagA-ab reported an increased risk for corpus atrophic gastritis whereas the combination of VL-PG, CagA-ab, IL-3954T, and IL*2/2 showed an increased risk for intestinal metaplasia (Table 4).

**Tests Characteristics of Combined Markers Associated with Gastric Premalignant Lesions.** Several combinations of markers showed improvement in the specificity rate and positive predictive value when compared with single markers. In particular, for detection of corpus atrophic gastritis, the specificity rate and positive predictive value of VL-PG were 80.7% and 39.3%, respectively, whereas those of a combination of VL-PG and CagA-ab increased to 92.7% and 62.2%, respectively (Table 5). For detection of intestinal metaplasia, the combination of L-PG, CagA-ab, IL-3954T, and IL*2/2 or VL-PG, CagA-ab, IL-3954T, and IL*2/2 considerably improved the specificity rate (96.7% and 99.5%, respectively) but dramatically decreased the sensitivity rate (21.7% and 17.4%, respectively) when compared with single markers. Other combinations of factors did not improve tests characteristics overall when compared with those of single markers.

**Seropositivity Rate of Each Marker Associated with Gastric Premalignant Lesions.** IL*2/2 reported the lowest seropositivity rate with 15.9%, followed by VL-PG with 27.4%, L-PG with 48.9%, IL-3954T with 54.6%, and CagA-ab with 66.4% (Table 6).

**Table 3. Sensitivity, specificity, positive predictive value and negative predictive value for detection of atrophic gastritis, corpus atrophic gastritis and intestinal metaplasia in Costa Rican dyspeptic patients.**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Se [% (95% CI)]</th>
<th>Sp [% (95% CI)]</th>
<th>PPV [% (95% CI)]</th>
<th>NPV [% (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of atrophic gastritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-PG</td>
<td>77.6 (66.0-89.2)</td>
<td>61.2 (53.5-69.0)</td>
<td>41.3 (31.6-51.0)</td>
<td>88.6 (82.3-94.9)</td>
</tr>
<tr>
<td>VL-PG</td>
<td>51.7 (38.0-65.4)</td>
<td>81.2 (75.0-87.5)</td>
<td>46.2 (35.8-62.6)</td>
<td>82.7 (76.6-88.9)</td>
</tr>
<tr>
<td>CagA-ab</td>
<td>82.8 (72.2-93.3)</td>
<td>51.5 (43.6-59.4)</td>
<td>37.5 (28.7-46.3)</td>
<td>89.5 (82.8-96.2)</td>
</tr>
<tr>
<td>Detection of corpus atrophic gastritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-PG</td>
<td>87.1 (73.7-100)</td>
<td>57.3 (50.0-64.6)</td>
<td>24.8 (16.2-33.3)</td>
<td>96.5 (92.7-100)</td>
</tr>
<tr>
<td>VL-PG</td>
<td>77.4 (61.1-93.8)</td>
<td>80.7 (74.9-88.6)</td>
<td>39.3 (26.3-52.4)</td>
<td>95.7 (92.2-99.1)</td>
</tr>
<tr>
<td>CagA-ab</td>
<td>90.3 (78.3-100)</td>
<td>47.9 (40.6-55.2)</td>
<td>21.9 (14.3-29.4)</td>
<td>96.8 (92.8-100)</td>
</tr>
<tr>
<td>Detection of intestinal metaplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VL-PG</td>
<td>78.3 (59.2-97.3)</td>
<td>78.5 (72.6-84.4)</td>
<td>29.5 (17.2-41.8)</td>
<td>96.9 (93.9-99.9)</td>
</tr>
<tr>
<td>CagA-ab</td>
<td>95.7 (85.1-100)</td>
<td>47.0 (39.8-54.2)</td>
<td>17.2 (10.3-24.1)</td>
<td>99.0 (96.4-100)</td>
</tr>
<tr>
<td>IL-3954T</td>
<td>80.0 (60.0-100)</td>
<td>48.9 (40.3-57.6)</td>
<td>18.4 (9.7-27.1)</td>
<td>94.4 (88.5-100)</td>
</tr>
<tr>
<td>IL*2/2</td>
<td>40.0 (16.0-64.0)</td>
<td>87.1 (81.1-93.0)</td>
<td>30.8 (11.1-50.4)</td>
<td>91.0 (85.7-96.2)</td>
</tr>
</tbody>
</table>

NOTE: ORs are adjusted for sex, age, and *H. pylori* seropositivity. *P < 0.001, vs controls.

*P < 0.05, vs controls.

**Table 4. ORs with 95% CIs for combinations of factors associated with atrophic gastritis, corpus atrophic gastritis, and intestinal metaplasia in Costa Rican patients.**

<table>
<thead>
<tr>
<th>Premalignant lesion</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic gastritis</td>
<td>L-PG, CagA-ab 6.3* (3.0-13.0)</td>
</tr>
<tr>
<td></td>
<td>VL-PG, CagA-ab 14.5* (5.8-36.4)</td>
</tr>
<tr>
<td>Corpus atrophic gastritis</td>
<td>L-PG, CagA-ab 13.6* (4.7-39.3)</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>L-PG, CagA-ab 38.6* (12.5-118.7)</td>
</tr>
<tr>
<td></td>
<td>IL-3954T, IL<em>2/2 7.1</em> (1.8-28.2)</td>
</tr>
<tr>
<td></td>
<td>VL-PG, CagA-ab, IL-3954T, IL<em>2/2 30.9</em> (3.0-318.9)</td>
</tr>
</tbody>
</table>

NOTE: ORs are adjusted for sex, age, and *H. pylori* seropositivity.
Discussion

In this study, we evaluated several markers as screening criteria to determine whether any of these factors, alone or combined, could effectively detect gastric premalignant lesions in a Costa Rican population.

The prevalence of *H. pylori* infection in this study was 74.4%, which is lower than that found in other Costa Rican studies (28, 29). High rates of *H. pylori* infection are common in developing countries (80-90%; refs. 30-32) and are usually associated with low socioeconomic status (33). We suggest that the socioeconomic status is one factor associated with the low prevalence of *H. pylori* infection in this study because the majority of the patients were of medium to high socioeconomic status (data not shown).

An age of more than 60 years was significantly associated with atrophic gastritis, corpus atrophic gastritis, and intestinal metaplasia, confirming that aging is considered to be linked with the process of chronic atrophic gastritis (34) and probably leading to subsequent metaplastic changes in the gastric mucosa.

Genetic factors such as male predominance or blood type A were not found to be associated with any premalignant lesions in this study (data not shown). This could be explained by the fact that these factors are generally thought to be associated with the diffuse histopathologic type of gastric cancer rather than the intestinal type (35, 36), and atrophic gastritis, corpus atrophic gastritis, and intestinal metaplasia are gastric premalignant lesions mainly considered as risk factors for developing the intestinal histopathologic type of gastric cancer (37).

After adjustment for age, sex, and *H. pylori* seropositivity, L-PG, VL-PG, and CagA-ab were associated with all gastric premalignant lesions and IL+3954T and IL*2/2 were associated with intestinal metaplasia, showing that several serologic markers effectively discriminated between affected and unaffected subjects in this study and could be considered as markers for detection of these premalignant lesions in the Costa Rican population.

An ideal marker would have both high sensitivity and specificity rates. Among the single markers evaluated, after adjustment for age, sex, and *H. pylori* seropositivity, for detection of any premalignant lesion, CagA-ab had the highest sensitivity rate but a very poor specificity rate. Due to this reason, and adding the fact that more than 70% of the *H. pylori*-positive subjects were positive for this marker, which coincides with a previous study (38), its use as a single marker does not seem to be suited for mass screening detection of gastric premalignant lesions in the Costa Rican population. VL-PG, with cutoff levels PG I ≤30 μg/L and PG I/II ratio ≤2, showed the best combination of test characteristics in this study (sensitivity, 77.4%; specificity, 80.7%; positive predictive value, 39.3%; negative predictive value, 95.7%), and by periodically testing these patients, an eventual increase in test characteristics is expected. VL-PG seemed to be a cost-effective marker because only 27.4% of the patients resulted positive for this marker, ensuring effectiveness while reducing the overall cost.

In the effort to improve test characteristics, we also investigated the influence of combined markers on the development of the premalignant lesions. Most of the combinations of markers including cytokine polymorphisms did not show overall improvement in test characteristics when compared with single markers because only the combination of VL-PG and CagA-ab for detection of corpus atrophic gastritis reported an increase in the specificity rate (92.7%) and positive predictive value (62.2%) combined with a considerable decrease in the seropositivity rate (16.6%) when compared with those of VL-PG alone. However, for the purpose of establishing a mass screening program in countries with economic restraints, it is essential to investigate if the combination of VL-PG with CagA-ab would be more cost-effective than periodic testing using VL-PG alone by analyzing if the improvement in test characteristics using the additional CagA-ab justifies the increase of laboratory burden and overall cost of the program. Moreover, in the case of severe atrophic gastritis, the living conditions of the *H. pylori* are depleted to such an extent that the bacteria may spontaneously disappear, eventually normalizing the *H. pylori* antibody and CagA-ab titers (39, 40). Therefore,

Table 5. Sensitivity, specificity, positive predictive value, and negative predictive value of combinations of factors for detection of atrophic gastritis, corpus atrophic gastritis, and intestinal metaplasia in Costa Rican dyspeptic patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>Se [% (95% CI)]</th>
<th>Sp [% (95% CI)]</th>
<th>PPV [% (95% CI)]</th>
<th>NPV [% (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of atrophic gastritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-PG, CagA-ab</td>
<td>63.8 (50.6-77.0)</td>
<td>81.2 (75.0-87.5)</td>
<td>54.4 (41.8-67.0)</td>
<td>86.5 (80.7-92.2)</td>
</tr>
<tr>
<td>VL-PG, CagA-ab</td>
<td>48.3 (34.6-62.0)</td>
<td>94.6 (90.8-98.3)</td>
<td>75.7 (60.5-90.9)</td>
<td>83.9 (78.3-89.4)</td>
</tr>
<tr>
<td>Detection of corpus atrophic gastritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-PG, CagA-ab</td>
<td>80.7 (65.1-96.2)</td>
<td>77.6 (71.5-83.8)</td>
<td>36.8 (24.6-49.0)</td>
<td>96.1 (92.8-99.5)</td>
</tr>
<tr>
<td>VL-PG, CagA-ab</td>
<td>74.2 (57.2-91.2)</td>
<td>92.7 (88.8-96.7)</td>
<td>62.2 (45.2-79.1)</td>
<td>95.7 (92.5-98.9)</td>
</tr>
<tr>
<td>Detection of intestinal metaplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-PG, CagA-ab, IL+3954T, IL*2/2</td>
<td>21.7 (2.7-40.8)</td>
<td>96.7 (93.9-99.6)</td>
<td>45.5 (11.5-79.4)</td>
<td>90.8 (86.5-95.1)</td>
</tr>
<tr>
<td>VL-PG, CagA-ab, IL+3954T, IL*2/2</td>
<td>17.4 (0.0-35.1)</td>
<td>99.5 (98.1-100)</td>
<td>80.0 (34.9-100)</td>
<td>90.6 (86.3-94.9)</td>
</tr>
</tbody>
</table>

Table 6. Seropositivity rate of serologic factors significantly associated with gastric premalignant lesions in Costa Rican dyspeptic patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>Seropositivity rate, pos/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-PG</td>
<td>109/223 (48.9)</td>
</tr>
<tr>
<td>VL-PG</td>
<td>61/223 (27.4)</td>
</tr>
<tr>
<td>CagA-ab</td>
<td>148/223 (66.4)</td>
</tr>
<tr>
<td>IL+3954T</td>
<td>113/207 (54.6)</td>
</tr>
<tr>
<td>IL*2/2</td>
<td>33/207 (15.9)</td>
</tr>
</tbody>
</table>

*With cutoff levels PG I ≤30 μg/L + PG I/II ≤3.
† With cutoff levels PG I ≤30 μg/L + PG I/II ≤2.
‡ Cytokine polymorphisms were successfully measured in 207 cases.
in some cases, the use of the CagA-ab status may misdiagnose premalignant lesions or gastric cancer itself.

Limitations of this study should be mentioned. First, the prevalence of H. pylori infection was lower than that in previous Costa Rican studies (28, 29), suggesting that the prevalence of gastric premalignant lesions could eventually be higher than that found in this study. However, the high prevalence of symptomatic patients >50 years of age could also lead to an overestimation of the detection of gastric premalignant lesions. Second, the analysis of factors was evaluated in a population with dyspeptic symptoms. We believe that if asymptomatic subjects were also included in the study, the seropositivity rate of the tests would probably decrease. We are currently evaluating the effectiveness of L-PG and VL-PG by targeting both symptomatic and asymptomatic subjects to clearly elucidate the effectiveness of the serum PG marker in the Costa Rican population. In the near future, we plan to correlate the serum PG status with corpus atrophic gastritis in gastric cancer cases to determine whether this method could effectively predict this cancer in the Costa Rican population.

Despite the limitations discussed above, this study shows that serum PG status alone or in combination with CagA-ab, for detection of corpus atrophic gastritis, seems to be the best suited method to identify subjects with a high-risk for gastric cancer in the Costa Rican population.

Acknowledgments
We thank Olympus America, Inc., Latin America Group for its support with gastric cancer detection and endoscopic equipment; Daniel Ribble for valuable comments; the technicians, anesthesiologists, and secretaries of the Centro Digestivo Doctores Con-Mediaplaza in San Jose, Costa Rica for technical and administrative assistance.

References


Cancer Epidemiol Biomarkers Prev 2007;16(12). December 2007
Serum Pepsinogen Levels, *Helicobacter pylori* CagA Status, and Cytokine Gene Polymorphisms Associated with Gastric Premalignant Lesions in Costa Rica

Sergio A. Con, Reinaldo Con-Wong, Gil R. Con-Chin, et al.


Updated version

Access the most recent version of this article at:

http://cebp.aacrjournals.org/content/16/12/2631

Cited articles

This article cites 39 articles, 7 of which you can access for free at:

http://cebp.aacrjournals.org/content/16/12/2631.full#ref-list-1

Citing articles

This article has been cited by 1 HighWire-hosted articles. Access the articles at:

http://cebp.aacrjournals.org/content/16/12/2631.full#related-urls

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.