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Helicobacter pylori infection and serum pepsinogen concentrations in an elderly population representative of Costa Rica

Infección por helicobacter pylori y concentraciones séricas de pepsinógenos en una población representativa de adultos de Costa Rica

Clas Une[1], Wendy Malespín Bendaña[2], Vanessa Ramírez-Mayorga[3], Luis Rosero-Bixby[4] y Rafaela Sierra Ramos[5]

Abstract: INTRODUCTION: Costa Rica has among the highest mortality rates from gastric cancer in the world, largely due to late detection. It is therefore important that economically and logistically sustainable screening is implemented in order to detect risk of developing cancer. We have previously shown that low pepsinogen (PG) values and infection with *Helicobacter pylori*-CagA+ are associated with risk of gastric atrophy and cancer in Costa Rican populations. **OBJECTIVES:** To determine how markers for gastric cancer risk are distributed in an elderly population representative of Costa Rica in order to design a screening strategy. **METHODS:** The population studied consists of 2,652 participants in a nationally representative survey of ageing. Information concerning epidemiologic, demographic, nutritional and life style factors is available. Serum PG concentrations as well as *H. pylori* and CagA status were determined by serology. Possible associations were determined by regression analyses. **RESULTS:** Antibodies to *H. pylori* were present in 72% of the population and of those, 58% were CagA positive. Infection with *H. pylori* was associated with higher PGI concentrations (p=0.000) and infection with *H. pylori*-CagA$^+$ with lower PGI concentrations (p=0.025). Both showed association with lower PGI/PGII (p=0.006 and p=0.000). Higher age was associated with lower prevalence of *H. pylori* infection (OR=0.98; p=0.000) and CagA$^+$ (OR=0.98; p=0.000) but not with PG values. Regions with high risk of gastric cancer showed lower PGI (p=0.004) and PGI/PGII values (p=0.021) as well as higher prevalence of *H. pylori* infection (OR=1.39; p=0.013) but not CagA$^+$. Using cut-off values of PGI<100 µg/L and PGI/PGII<2.0, 2.5 and 3.0, 7-15% of the population would be considered at risk. **CONCLUSIONS:** *H. pylori* alone is not a useful marker for risk of gastric cancer. Screening using serum pepsinogen concentrations and infection with *H. pylori*-CagA$^+$ is feasible in the general elderly population of Costa Rica but appropriate cut-off values have to be determined based on more clinical data and follow up capacity.

Key words: gastric cancer, atrophic gastritis, pepsinogens, Helicobacter pylori

[1] Institute of Health Research (INISA), University of Costa Rica, San José, COSTA RICA Correo: allan.une@ucr.ac.cr ORCID ID: https://orcid.org/0000-0003-3708-7392

[2] Institute of Health Research (INISA), University of Costa Rica, San José, COSTA RICA Correo: wkmalespinb@gmail.com ORCID ID: https://orcid.org/0000-0002-1466-4815

[3] Institute of Health Research (INISA), University of Costa Rica, San José, COSTA RICA Correo: vanessa.ramirez@ucr.ac.cr ORCID ID: https://orcid.org/0000-0003-4104-3261

[4] Central American Center for Population Studies, University of Costa Rica, San José, COSTA RICA Correo: lrosero@mac.com ORCID ID: https://orcid.org/0000-0002-3063-3111

[5] Institute of Health Research (INISA), University of Costa Rica, San José, COSTA RICA Correo: sierra.rafaela@gmail.com ORCID ID: https://orcid.org/0000-0003-4712-7503

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Resumen: INTRODUCCIÓN: Costa Rica tiene una de las tasas de mortalidad por cáncer gástrico más altas del mundo, en gran parte debido a la detección tardía. Por lo tanto, es importante que se implemente un tamizaje económico y logísticamente sostenible para detectar el riesgo de desarrollar cáncer. En estudios anteriores demostramos, que valores bajos de pepsinógeno (PG) y la infección por Helicobacter pylori-CagA+ están asociados con el riesgo de atrofia gástrica y cáncer en poblaciones costarricenses. **OBJETIVO**: Determinar cómo se distribuyen los marcadores de riesgo de cáncer gástrico en una población representativa de adultos de Costa Rica para diseñar una estrategia de tamizaje. **MÉTODOS**: Se estudió una población representativa a nivel nacional de 2.652 adultos, que formaron parte de un estudio longitudinal sobre envejecimiento. Se dispone de información sobre factores epidemiológicos, demográficos, nutricionales y de estilo de vida. Las concentraciones séricas de PG, así como el estado de H. pylori y CagA se determinaron mediante serología. Las posibles asociaciones se determinaron mediante modelos de regresión (logística y lineal múltiple). **RESULTADOS**: El 72% de la población presenta anticuerpos contra H. pylori, de ellos, el 58% fueron positivos para CagA. La infección por H. pylori se asoció con altas concentraciones de PGI (p = 0,000) y la infección por H. pylori-CagA+ con bajas concentraciones de PGI (p = 0,025). Ambas pruebas mostraron asociación con una baja razón PGI/PGII (p = 0,006 y p = 0,000). El rango de mayor edad se asoció con una menor prevalencia de la infección por H. pylori (OR = 0,98; p = 0,000) y de CagA+ (OR = 0,98; p = 0,000) pero no se asoció con los valores de PG. Las regiones con alto riesgo de CG mostraron valores bajos de PGI (p = 0,004) y de PGI/PGII (p = 0,021) así como una alta prevalencia de la infección por H. pylori (OR = 1,39; p = 0,013), no así con CagA+. Utilizando valores de corte de PGI<100 µg/L y de PGI/PGII <2,0, 2,5 y 3,0, se consideraría en riesgo de cáncer entre 7-15% de la población. **CONCLUSIONES**: La infección por H. pylori, por sí sola, no es un marcador de riesgo de CG útil. Es factible realizar el tamizaje de adultos de la población general de Costa Rica, utilizando como marcadores las concentraciones séricas de pepsinógenos y la infección por H. pylori-CagA+, sin embargo, los valores de corte apropiados deben determinarse con base en una mayor cantidad de datos clínicos y la capacidad de seguimiento.

Palabras clave: cáncer gástrico, gastritis atrófica, pepsinógenos, Helicobacter pylori

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1. Introduction

Gastric carcinogenesis is a well-established process that starts with superficial gastritis which evolves into atrophy, metaplasia, dysplasia and finally adenocarcinoma (Correa, 1992). The whole process takes decades and is, in most cases, initiated by infection with *Helicobacter pylori (*Graham, 1997; Persson et al., 2011). *H. pylori* infects the gastric mucosa and induces an inflammation that normally persists for life, if untreated. About 50% of the world's population is infected. However, only a small portion proceeds to develop cancer. The final result of *H. pylori* infection depends on complex and largely unknown interactions between the characteristics of the infecting strain, host genetics, immune status, and environmental factors. Thus, infection with bacteria expressing certain virulence factors, most prominently the cytotoxin-associated protein A (CagA) have been associated with increased risk of cancer and other gastric pathologies (Parsonnet, Friedman, Orentreich y Vogelman,

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1997; Blaser et al., 1995; Yamaoka, 2010; Park, Forman, Waskito, Yamaoka y Crabtree, 2018). In the host, gene polymorphisms associated with an exacerbated inflammatory response can also increase the risk of cancer (El-Omar et al., 2000; Taguchi et al., 2005; Alpízar-Alpízar, Pérez-Pérez, Une, Cuenca y Sierra, 2005). Among the environmental risk factors are low intake of foodstuffs containing antioxidants and high salt intake (Crew y Neugut, 2006; Fox et al., 1999; Menaker, Sharaf y Jones, 2004).

The symptoms of precancerous lesions and early gastric tumors are similar to common symptoms of gastric disease and therefore the patient often does not seek medical attention in time, with the result that most cancers are diagnosed at an advanced stage of the disease when treatment is likely to fail. However, if detected at an early stage, the patient can be cured by eliminating the tumor.

Considerable efforts have been made to identify markers that indicate the presence of precancerous lesions or early tumors. The most promising ones so far have been pepsinogens and gastrin (Dinis-Ribeiro, Yamaki, Miki y Costa-Pereira, 2004; Cao, Ran y Xiao, 2007).

Costa Rica has among the highest mortality rates from gastric cancer in the world, largely due to late detection(Sung et al., 2021)). It is therefore important that economically and logistically sustainable screening is implemented in order to detect risk of developing cancer. We have previously shown that low pepsinogen (PG) values and infection with *H. pylori*-CagA+ are associated with risk of gastric atrophy and cancer in Costa Rican populations (Sierra et al., 2003; Sierra et al., 2006; Sierra et al., 2008). This study was undertaken to evaluate the feasibility of implementing the ABCD method in the Costa Rican population. For this purpose we took advantage of an existing survey of ageing involving 2671 participants >60 years old and representative of the whole country (Brenes-Camacho y Rosero-Bixby, 2008).

Pepsinogen concentrations and *H. pylori* infection were assessed and the participants were classified into the ABCD categories using different cut-off points. The number of people considered at risk and therefore eligible for endoscopy was calculated. The additional value of aggregating CagA positivity to the scheme was addressed. Also, the associations of *H. pylori* infection and pepsinogen levels to demographic and socioeconomic parameters were analyzed.

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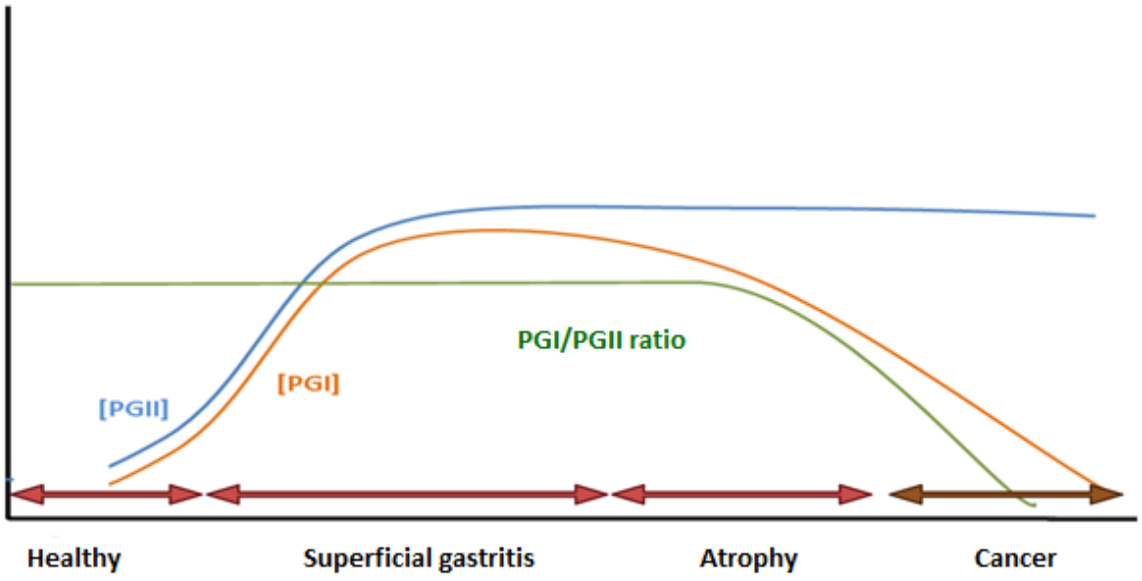
2. Theoretical framework

Methods of screening for risk of gastric cancer: Pepsinogens (PG) are precursors of pepsin produced in the gastric mucosa and secreted into the lumen. A small amount, however, escapes into the bloodstream and the two types, PGI and PGII, can be readily quantified by serology (Brenner, Rothenbacher y Weck, 2007; Sipponen, Härkönen, Alanko y Suovaniemi, 2003). Gastric inflammation and atrophy alter the expression pattern of pepsinogens and these changes are reflected in blood concentrations where low PGI levels and low PGI/PGII ratios are related to atrophy, particularly in the gastric body (Figure 1). This is considered a precancerous lesion and blood PG concentrations can be used to screen for risk of gastric cancer (Sipponen, Samloff, Saukkonen y Varis, 1985).

Figure 1.

Serum pepsinogen levels during gastric carcinogenesis.



H. pylori, *H. pylori*-CagA+: There are several methods to determine if a person is infected with *H. pylori*, including histology, rapid urea test, urea breath test or stool tests. However, these are invasive, complicated, and/or expensive. The most feasible way is to determine the presence of serum antibodies to H. pylori, which is a low-cost, non-invasive method that is especially useful in larger populations. Although H. pylori infection is strongly associated with gastric cancer, it is not by itself an indicator of risk because the large majority of infected people will not develop cancer.

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However, infection status can be used together with other blood markers, such as pepsinogen levels, to increase the specificity.

H. pylori expresses a number of virulence factors, the most prominent being CagA. Infection with H. pylori expressing CagA increases the risk of cancer substantially. Whereas the detection of other virulence markers requires a genetic analysis, and therefore an invasive procedure to isolate the bacteria from the stomach, people infected with CagA positive strains can be readily identified by measuring serum antibodies to CagA. Thus, *H. pylori*, CagA, and pepsinogens can be analyzed from the same blood sample.

ABCD method: Miki et al. have proposed a combined assay (the ABCD method) for serum anti-*H. pylori* IgG antibody and serum pepsinogen levels to screen for gastric cancer-risk (Miki, 2011). Subjects are classified into one of four risk groups: A: [*H. pylori*(-) PG(high)], healthy; B: [*H. pylori*(+) PG(high)], healthy or mild chronic atrophic gastritis (CAG); C: [*H. pylori*(+) PG(low)], CAG; D: [*H. pylori*(-) PG(low)], severe CAG. By this scheme, endoscopic examination should be compulsory for group C and D whereas group A and B can be excluded.

3. Popularion and methods

3.1 Population

The sample individuals in this study come from the Costa Rican study of Longevity and Healthy Aging (CRELES, for its name in Spanish). This is a longitudinal study of a nationally representative sample of 2827 adults ages 60 years and over. Detailed information of CRELES has been published elsewhere (Méndez-Chacón, Santamaría-Ulloa y Rosero-Bixby, 2008). The database of CRELES contains self-reported health status, sociodemographic, anthropometric, nutritional, life style and clinical laboratory data. The analytic sample size with valid information for PG, *H. pylori* and CagA is 2652 individuals aged 60 to 109 years. Because of the CRELES sample design, older individuals are oversampled in this data set.

All participants provided informed consent. The University of Costa Rica Ethics Committee approved the procedure for collecting data and the informed consent form.

3.2 *Helicobacter pylori* serology

Serum antibodies to *H. pylori* were measured in a qualitative Enzyme Linked Immunosorbent Assay (ELISA) developed in our laboratory and based on a modification of a previously described ELISA

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(Perez-Perez, Dworkin, Chodos y Blaser, 1988; Méndez-Chacón, Ramírez, Malespín-Bendaña, Pérez-Pérez, y Une, 2020).

3.3 CagA serology

Serum antibodies to CagA were measured by ELISA as described by Blaser *et al*. 1995(5).

3.3.1. Serum pepsinogen concentrations

Serum concentrations of PGI and PGII were determined by ELISA (BiohitOyj, Finland) according to the manufacturer's instructions.

3.4 Socio-demographic characteristics and control variables

The following characteristics of individuals in the sample were including in the analysis mostly as control variables: Sex (1 = male 0 = female), age (exact years), years of education attainment, rural dwelling, and community's risk of gastric cancer according to the national cancer registry (low risk = 25% cantons with the lowest incidence rate; high risk = 25% cantons with the highest incidence rate).

3.5 Statistical analysis

All statistical analysis was performed using the STATA software (version!). Logistic regression models estimated the odds ratios (ORs) and 95% confidence intervals (CI 95%) for *H. pylori*+ *and* CagA+ by comparing the seropositive and negative groups with adjustment for the aforementioned control variables. The level of significance was set at $p<0.05$. Multiple lineal regression models were used to determine possible effects on blood pepsinogen concentrations from *H. pylori* interacting with CagA+ with adjustment for the above-mentioned control variables.

4. Results

4.1 *H. pylori* infection

Antibodies to *H. pylori* were present in 72% of the population and 49% were seropositive for CagA. Of the *H. pylori* positive participants, 58% had serum antibodies to CagA (Table 1).

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Increased age and more years of education were factors associated with lower risk of *H. pylori* infection (Table 2). In addition, living in areas with high risk of gastric cancer increased the risk of being seropositive for *H. pylori* but, interestingly, not with *H. pylori*-CagA.

CagA seropositivity decreased with higher age (Table 2) and this was not only an effect of the lower prevalence of *H. pylori* because a significant inverse association between CagA and age was seen also when only the *H. pylori* positive subpopulation was analyzed (data not shown). Like *H. pylori*, CagA was inversely associated with education and people living in rural areas were more likely to be infected with CagA positive strains (Table 2).

4.2 Blood pepsinogens

Infection with *H. pylori* was associated with higher PGI concentrations. Infection with *H. pylori* strains carrying CagA showed association with lower PGI/PGII (Table 3). Higher age was not associated with neither PGI nor PGI/PGII. Regions with high risk of gastric cancer showed lower PGI and PGI/PGII values.

4.3 Definition of risk groups

A previous study in our laboratory showed that the optimal cut-off points for detection of adenocarcinoma in a high-risk group by pepsinogen concentrations were PGI<60▪g/L and PGI/PGII<2.5(Sierra et al., 2003). The manufacturer of the PG kits recommends a cut-off point of PGI/PGII<3 for detection of advanced corpus atrophy and increased risk of gastric cancer. In order to assess the quantity of people that would potentially be referred to endoscopic examination based on the results of the PG test, three different cut-off points were applied: PGI/PGII<2, <2.5 and <3. Within this range, very few cases of high PGI concentrations were found and the cut-off for PGI was set at <100μg/L in all cases.

The percentage of participant in each group A-D is shown in Table 4. About two thirds of the population fit in group B with a healthy PG profile but infected with *H. pylori*.

The two highest risk groups, C and D were relatively small, and therefore combined as the group potentially eligible for follow up with endoscopy. By this standard, 7-14% of the population would be in the high-risk group, depending on the choice of cut-off point.

The age and sex distributions of the risk groups were similar to those of the whole population (Table 5). However, the population at risk had lower prevalence of *H. pylori* infection. The risk groups defined by the different cut-off points did not differ significantly between them with respect to these characteristics (Table 5).

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5. Discussion

It is known from several studies that *H. pylori* infect the majority of Costa Ricans (Alpízar-Alpízar et al., 2005; Sierra et al., 2006; Sierra et al., 1992). A global trend is that prevalence increases with age. This is believed to be a cohort effect reflecting decreased transmission rates with each generation due to improved hygiene and socioeconomic factors such as less crowded living conditions. The prevalence of 72% in this general population is not surprising. Earlier studies have shown a prevalence of around 90% in dyspeptic and high-risk populations (Sierra et al., 2006; Ferrer-Ferrer, 2013). A lower prevalence, 56%, was observed among a group of employees at the University of Costa Rica, a younger population with better socioeconomic standard (unpublished results).

In this context, an unexpected result was that *H. pylori* infection is less common with increased age. There are several possible explanations for this. With age, the stomach becomes more atrophic, providing a less hospitable habitat for the bacteria. This could lead to decreased bacterial densities that, together with the deteriorating immune status of the aging host, push the levels of antibodies to *H. pylori* below the cut-off points of the assay. Another possibility is that *H. pylori,* the harmful effects of which are more pronounced later in life (Atherton, y Blaser, 2009), is associated with higher mortality and that the decrease in prevalence with age is a survivor effect. The observation that infection with CagA expressing strains follows the same pattern of decrease with age is consistent with both these explanations given that the higher virulence can be assumed to cause more atrophy and higher mortality. An alternative explanation is that the higher infection at younger ages is a cohort effect; meaning that younger generations, for some unknown reason, are more exposed to *H. pylori* infection. However, with the cross-sectional data of this study is not possible to disentangle cohort from age effects.

H. pylori infection is known to depend on socioeconomic status in the sense that poverty and conditions associated with poverty promote infection (Boffetta, 1997; Lee, 2007). The results confirm this, as more years of education, which is associated with higher living standard, resulted in lower risk for infection. This was also the case for virulence because CagA showed an inverse association with education. CagA, on the other hand was associated with living in rural zones whereas *H. pylori* was not. So, a rather complex picture emerges where *H. pylori* infection is more prevalent in populations with less education and in high-risk zones and virulence, as represented by CagA expression, is more accentuated in rural areas. In order to attempt to understand this pattern, a more detailed analysis of subgroups will be required.

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Blood PGI levels typically increase with *H. pylori* infection and decrease when atrophy develops (Sipponen et al., 1985). In this sample, *H. pylori* seropositivity was associated with increased PGI concentrations. This is consistent with the notion that the non-atrophic inflammation initially provoked by *H. pylori* is accompanied by increased PGI secretion. At the same time, *H. pylori* infection was associated with a significantly lower PGI/PGII ratio. That would be the case if PGII secretion, as expected, is also boosted by mild inflammation and keeps the ratio down in spite of increased PGI. Contrary to *H. pylori* alone, CagA was associated with significantly lower blood PGI levels, suggesting that CagA expressing strains are more prone to cause severe atrophic lesions characterized by partial loss of PGI producing glands. Furthermore, CagA was strongly associated with a decrease in PGI/PGII as would be expected with severe atrophy when much of the PGI production has been suppressed but PGII, produced in unaffected parts of the stomach remains high. We have previously shown in a dyspeptic population that a low PGI/PGII ratio is associated with atrophic gastritis, especially of the gastric body, which is considered a precancerous lesion (Sierra et al., 2006; Sierra et al., 2008; Sipponen et al., 1985). It was shown in the same population that CagA was associated with atrophic gastritis as well as with lower PGI levels and PGI/PGII values (Sierra et al., 2008). A limitation of this study is that, as endoscopy could not be performed, the true condition of the gastric mucosa is not known. However, the PG data are consistent with the expected pattern suggesting that the application of PG testing in this population is valid.

PG levels did not decrease with age. Others have reported that aging is accompanied by atrophy (Plebani, 1993; Lin, 2014; Shan, Bai, Han, Yuan y Sun, 2017). However, in the dyspeptic population mentioned above, age did not significantly influence the concentrations of PGs in blood although lower PGI/PGII levels came close to significance for subjects >50 years (Sierra et al., 2008). The reason for the lack of association could be that all the participants were over 60 years old. It is possible that an age-association would have been detected if younger people had been included.

The PGI/PGII ratio was clearly lower in high-risk zones. This was also true of PGI concentrations. This has to be interpreted as a strong indication of more extensive gastric atrophy in these populations, compared to those residing in low-risk zones. Interestingly, the effect was equally pronounced when adjusted for *H. pylori* and CagA, suggesting that other factors contribute to the high incidence of gastric cancer even if infection with *H. pylori* may be required.

In areas with high risk of gastric cancer, *H. pylori* infection was more prevalent. This finding contradicts an earlier study from this lab where prevalence was similar in selected high and low-risk zones (Sierra et al., 1993). This discrepancy may be explained by the more limited areas and smaller size of sample in the previous study. It should be mentioned, however, that in a population recruited in the province of Cartago, a high-risk zone, for a study of early detection of gastric cancer, the

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prevalence of *H. pylori* infection was notably high, 89% (Alpízar-Alpízar et al., 2005). That population was not selected by standards of any known risk factor except for residing in a high-risk zone. Nevertheless, infection with CagA-expressing strains was not more common in high-risk zones and can thus not explain the risk of gastric cancer or the higher degree of atrophy indicated by the pepsinogen data. It is likely that the high prevalence of *H. pylori* infection in high-risk zones is not a causal factor for the high incidence of cancer but rather associated with other characteristics, yet to be elucidated, of these areas.

In populations with low prevalence of *H. pylori* infection it is feasible to refer all subjects from groups B to D, i.e. all those infected and all those with low PGs, to endoscopic examination (Miki, 2011). In the population studied here this is not possible as more than 80% would fall into those categories, primarily due to the high infection rate. Instead, we considered eligible for endoscopy only groups C and D, that is all those with low PGs irrespective of *H. pylori* status. This resulted in an estimated 7-14% "at risk". Right now, there is about 40000 people aged 60 in Costa Rica. A screening at this age, and only at this age, would thus require 3000-6000 endoscopic examinations per year. Of course, this is an unlikely scenario. Not everyone will undergo screening and accept endoscopy. It may be preferable to do the screening several times. If screening is focused on high-risk areas, a higher percentage will be "at risk". Most likely, screening at a younger age would improve the sensibility. It has been argued that the ABCD method is less efficient when age-associated gastric atrophy is widespread (Shimoyama et al., 2012)).Before implementing a screening protocol, these factors have to be evaluated in each setting, as well as the follow-up capacity of the local health care systems.

The high age of participants in this study is a limitation for using its results, given that screening for gastric cancer risk would typically initiate before the age of 60. A younger sample might generate different results. Also, more analyses of PG concentrations in the blood of cancer patients, individuals with precancerous lesions and healthy controls are needed to better define appropriate cut-off points.

In conclusion, infection with *H. pylori* is not a useful marker for risk of gastric cancer, given that people with PG concentrations below the cut-off points actually had lower prevalence of *H. pylori* infection than the population as a whole. Serology for CagA could be of more utility since CagA is clearly associated with atrophy, but as CagA may thus not be an independent marker, and because it is not associated with high-risk areas, the aggregated value of including it in a screening has to be evaluated. The best candidate marker seems to be a low PGI/PGII ratio which is associated with high-risk areas and has been shown to associate with both atrophy and cancer. PGI values strongly follow the ratio and do not add any precision to the test. Furthermore, it may be preferable to

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perform pepsinogen screening for gastric cancer at an earlier age than 60 years given that atrophy increases at advanced ages, irrespective of *H. pylori* status, and this could result in more false positives. Also, the development of gastric adenocarcinoma is a prolonged process and successful treatment is highly dependent on early detection. Thus, detection at younger ages would improve the chances of survival.

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7. Referencias

Alpízar-Alpízar, W., Pérez-Pérez, G.I., Une, C., Cuenca, P. and Sierra, R. (2005). Association of interleukin-1B and interleukin-1RN polymorphisms with gastric cancer in a high-risk population of Costa Rica. *Clin Exp Med., 5*(4), 169-76.

Atherton, J.C. and Blaser, M.J. (2009). Coadaptation of Helicobacter pylori and humans: ancient history, modern implications. *J Clin Invest.,119*(9), 2475-87.

Blaser, M.J., Perez-Perez, G.I., Kleanthous, H., Cover, T.L., Peek, RM, Chyou, P.H., Nomura, A. (1995). Infection with Helicobacter pylori strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach. *Cancer Res., 55*(10), 2111-5.

Brenes-Camacho, G. and Rosero-Bixby, L. (2008). Metabolic control in a nationally representative diabetic elderly sample in Costa Rica: patients at community health centers vs. patients at other health care settings. *BMC Int Health Hum Rights., 8*, 5.

Brenner, H., Rothenbacher, D. and Weck, M.N. (2007). Epidemiologic findings on serologically defined chronic atrophic gastritis strongly depend on the choice of the cutoff-value. *Int J Cancer, 121*(12), 2782-6.

Doi: https://doi.org/10.15517/psm.v0i19.49405
19, número 2, Art. Cient. enero-junio 2022

Boffetta, P. (1997). Infection with Helicobacter pylori and parasites, social class and cancer. *IARC Sci Publ,* (138), 325-9.

Cao, Q., Ran, Z.H. and Xiao, S.D. (2007). Screening of atrophic gastritis and gastric cancer by serum pepsinogen, gastrin-17 and Helicobacter pylori immunoglobulin G antibodies. *J Dig Dis., 8*(1), 15-22.

Correa, P. (1992) Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res., 52*(24), 6735-40.

Crew, K.D. and Neugut, A.I. (2006). Epidemiology of gastric cancer. *World J Gastroenterol, 12(*3), 354-62.

Dinis-Ribeiro, M., Yamaki, G., Miki, K. y Costa-Pereira, A., Matsukawa M, and Kurihara M. (2004). Meta-analysis on the validity of pepsinogen test for gastric carcinoma, dysplasia or chronic atrophic gastritis screening. *J Med Screen, 11*(3), 141-7.

El-Omar, E.M., Carrington, M., Chow, W.H., McColl, K.E., Bream, J.H., Young, H.A., and Rabkin, C.S. (2000). Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature, 404*(6776), 398-402.

Ferrer-Ferrer, M., Malespín-Bendaña, W., Ramírez, V., González, M.I., Carvajal, A. and Une, C. (2013). Polymorphisms in genes coding for HSP-70 are associated with gastric cancer and duodenal ulcer in a population at high risk of gastric cancer in Costa Rica. *Arch Med Res, 44*(6), 467-74.

Fox, J.G., Dangler, C.A., Taylor, N.S, King, A., Koh, T.J. and Wang, T.C. (1999). High-salt diet induces gastric epithelial hyperplasia and parietal cell loss, and enhances Helicobacter pylori colonization in C57BL/6 mice. *Cancer Res., 59*(19), 4823-8.

Graham, D.Y. (1997) *Helicobacter pylori* infection in the pathogenesis of duodenal ulcer and gastric cancer: a model. *Gastroenterology, 113*(6), 1983-91.

Lee, A. (2007). Early influences and childhood development. Does Helicobacter play a role? *Helicobacter, 12*(Suppl 2), 69-74.

Lin, J.T. (2014). Screening of gastric cancer: who, when, and how. *Clin Gastroenterol Hepatol, 12*(1), 135-8.

Menaker, R.J., Sharaf, A.A. y Jones, N.L. (2004) Helicobacter pylori infection and gastric cancer: host, bug, environment, or all three? *Curr Gastroenterol Rep., 6*(6), 429-35.

Méndez-Chacón, E., Ramírez, V., Malespín-Bendaña, W., Pérez-Pérez, G. and Une, C. (2020). Validación de una prueba serológica para detectar la infección por Helicobacter pylori en Costa Rica. *Revista de Biología Tropical, 68*, 551-62.

ISSN-1659-0201
http://ccp.ucr.ac.cr/revista/

Doi: https://doi.org/10.15517/psm.v0i19.49405
19, número 2, Art. Cient. enero-junio 2022

Méndez-Chacón, E., Santamaría-Ulloa, C. and Rosero-Bixby, L. (2008). Factors associated with hypertension prevalence, unawareness and treatment among Costa Rican elderly. *BMC Public Health, 8*, 275.

Miki, K. (2011). Gastric cancer screening by combined assay for serum anti-Helicobacter pylori IgG antibody and serum pepsinogen levels - "ABC method". *Proc Jpn Acad Ser B Phys Biol Sci., 87*(7), 405-14.

Park, J.Y., Forman, D., Waskito, L.A., Yamaoka, Y. and Crabtree, J.E. (2018). Epidemiology of. *Toxins (Basel), 10*(4), 163. doi: 10.3390/toxins10040163

Parsonnet, J., Friedman, G.D., Orentreich, N. and Vogelman, H. (1997). Risk for gastric cancer in people with CagA positive or CagA negative Helicobacter pylori infection. *Gut., 40*(3), 297-301

Perez-Perez, G.I., Dworkin, B.M., Chodos, J.E. and Blaser, M.J.(1988). Campylobacter pylori antibodies in humans. *Ann Intern Med.,109*(1), 11-7.

Persson, C., Jia, Y., Pettersson, H., Dillner, J., Nyrén, O. and Ye, W. H. (2011). *H. pylori* seropositivity before age 40 and subsequent risk of stomach cancer: a glimpse of the true relationship? *PLoS One, 6*(3), e17404.

Plebani, M. (1993). Pepsinogens in health and disease. *Crit Rev Clin Lab Sci., 30*(3), 273-328.

Shan, J.H., Bai, X.J., Han, L.L., Yuan, Y. and Sun, X.F. (2017). Changes with aging in gastric biomarkers levels and in biochemical factors associated with. World J Gastroenterol.23(32):5945-53.

Shimoyama, T., Aoki, M., Sasaki, Y., Matsuzaka, M., Nakaji, S. and Fukuda, S. (2012). ABC screening for gastric cancer is not applicable in a Japanese population with high prevalence of atrophic gastritis. *Gastric Cancer, 15*(3), 331-4.

Sierra, R., Chinnock, A., Ohshima, H., Pignatelli, B., Malaveille, C., Gamboa, C.,and Bartsch, H. (1993). In vivo nitrosoproline formation and other risk factors in Costa Rican children from high- and low-risk areas for gastric cancer. *Cancer Epidemiol Biomarkers Prev., 2*(6), 563-8.

Sierra, R., Une, C., Ramirez, V., Alpizar-Alpizar, W., Gonzalez, M.I., Ramirez, J.A., and Megraud, F. (2008). Relation of atrophic gastritis with Helicobacter pylori-CagA(+) and interleukin-1 gene polymorphisms. *World J Gastroenterol, 14*(42), 6481-7.

Sierra, R., Une, C., Ramírez, V., González, M.I., Ramírez, J.A., de Mascarel, A., and Megraud, F. (2006). Association of serum pepsinogen with atrophic body gastritis in Costa Rica. *Clin Exp Med., 6*(2), 72-8.

Sierra, R., Mena, F., Ramírez, V., Méndez, E., Salazar, M., Une, C., and Kajiwara, T. (2003). Pepsinógenos séricos para detectar cáncer gástrico en Costa Rica. *Acta Bioquímica Clínica Latinoamericana, 37*(4), 357-62.

ISSN-1659-0201
http://ccp.ucr.ac.cr/revista/

Doi: https://doi.org/10.15517/psm.v0i19.49405
19, número 2, Art. Cient. enero-junio 2022

Sierra, R., Muñoz, N., Peña, A.S., Biemond, I., van Duijn, W. and Lamers, C.B.(1992). Antibodies to *Helicobacter pylori* and pepsinogen levels in children from Costa Rica: comparison of two areas with different risks for stomach cancer. *Cancer Epidemiol Biomarkers Prev., 1*(6), 449-54.

Sipponen, P., Härkönen, M., Alanko, A. and Suovaniemi, O. (2003). Diagnosis of atrophic gastritis from a serum sample. *Minerva Gastroenterol Dietol, 49*(1),11-21.

Sipponen, P., Samloff, I.M., Saukkonen, M. and Varis, K.. (1985). Serum pepsinogens I and II and gastric mucosal histology after partial gastrectomy. *Gut., 26*(11), 1179-82.

Sung, H., Ferlay, J.Siegel, R.L.,Laversanne, M., Soerjomataram, I. and Jemal, A.(2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin., 71*(3), 209-49.

Taguchi, A., Ohmiya, N., Shirai, K., Mabuchi, N., Itoh, A. and Hirooka, Y. (2005). Interleukin-8 promoter polymorphism increases the risk of atrophic gastritis and gastric cancer in Japan. *Cancer Epidemiol Biomarkers Prev., 14*(11 Pt 1), 2487-93.

Yamaoka, Y. (2010) Mechanisms of disease: *Helicobacter pylori* virulence factors. *Nat Rev Gastroenterol Hepatol, 7(*11), 629-41.

ISSN-1659-0201
http://ccp.ucr.ac.cr/revista/

Doi: https://doi.org/10.15517/psm.v0i19.49405
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8. Annexes

Table 1
Characteristics of the sample studied

Characteristics	Total
Males/Females	1213/1439
Averageage ±SD	76.8±10.6
Averageeducationyrs±SD	4.0±3.7
Stomach pain yes/no	690/1957
Rural/urban dwelling	1068/1584
Region's gastric cancer risk low/medium/high	584/1441/627
H. pylori+, n (%)	1921 (72%)
CagA+, n (%)	1298(49%)
CagA+/*H. pylori*+, n (%)	1117 (58%)
Mean PGI (▪ g/L)±SD	124.7±74.6
Mean PGII (▪ g/L)±SD	16.7±8.7
Mean PGI/PGII±SD	8.32±6.99

Table 2.

Odds ratios with 95% confidence intervals for the association of seropositivity for *H. pylori* and CagA with characteristics of the population

	H. pylori		CagA	
	OR (95%CI)	p	OR (95%CI)	p
Male (ref. Female)	1.22 (1.02-1.45)	0.026	1.16(1.00-1.36)	0.056
Age (years)	0.98 (0.97-0.99)	0.000	0.98 (0.97-0.98)	0.000
Education (years)	0.97 (0.94-0.99)	0.016	0.97 (0.95-0.99)	0.004
Rural dwelling (ref. urban)	0.96 (0.80-1.16)	0.701	1.23(1.04-1.46)	0.014
Low community's gastric cancer	1.0		1.0	
Medium community's gastric cancer	1.18(0.95-1.46)	0.128	1.16(0.95-1.42)	0.133
High community's gastric cancer	1.39(1.08-1.80)	0.011	0.98 (0.78-1.24)	0.886

N observations = 2,652

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Table 3.

Multiple lineal regression analysis for the association of blood concentrations of PGI and the ratio PGI/PGII with characteristics of the population

Factor variable	PGI μ/L			PGI/PGII ratio		
	Coeff.	(95% C.I.)	p	Coeff.	(95% C.I.)	p
H. pylori- &CagA-	0.0	Reference		0.0	Reference	
H. pylori- &CagA+	7.8	(-4.6 to 20.1)	0.219	-1.0	(-2.2 to 0.1)	0.081
H. pylori+ &CagA-	34.9	(27.0 to 42.9)	0.000	0.0	(-0.8 to 0.7)	0.961
H. pylori+ &CagA+	23.9	(16.3 to 31.5)	0.000	-1.8	(-2.6 to -1.1)	0.000
Being male	-2.9	(-8.5 to 2.8)	0.320	0.3	(-0.3 to 0.8)	0.335
Age (years)	0.0	(-0.3 to 0.3)	0.882	0.0	(0.0 to 0.0)	0.081
Education (years)	0.6	(-0.2 to 1.4)	0.174	0.0	(-0.1 to 0.1)	0.715
Rural dwelling (ref. urban)	4.8	(-1.3 to 10.9)	0.123	-0.2	(-0.8 to 0.3)	0.417
Community's gastric cancer risk						
Low	0.0	Reference		0.0	Reference	
Medium	-5.6	(-12.8 to 1.6)	0.127	-1.1	(-1.8 to -0.4)	0.001
High	-14.7	(-23.1 to -6.4)	0.001	-2.2	(-3.0 to -1.4)	0.000

N observations = 2,652

Table 4.

Distribution of the population in risk groups by different cut-off points

Risk groups	PGI<100 PGI/PGII<2.0	PGI<100 PGI/PGII<2.5	PGI<100 PGI/PGII<3.0
A: *H.pylori*-, PG high	24.3%	23.4%	22.7%
B: *H.pylori*+, PG high	68.0%	66.0%	64.1%
C: *H.pylori*+, PG low	4.4%	6.3%	8.2%
D: *H.pylori*-, PG low	3.3%	4.2%	5.0%

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Table 5.

Percentage in high risk groups (C + D) by selected characteristics and different cut-off points

Characteristics	PGI<100 PGI/PGII<2.0	PGI<100 PGI/PGII<2.5	PGI<100 PGI/PGII<3.0
Sex			
Female	7.7	10.4	12.7
Male	7.7	10.7	13.7
Age			
60-69	5.7	8.5	10.4
70-79	8.8	10.6	13.6
80-109	8.4	12.1	14.9
Community's gastric cancer risk			
Low	6.5	8.6	11.1
Medium	7.0	9.9	12.3
High	10.5	13.9	17.1
H. pylori			
Negative	12.0	15.3	17.8
Positive	6.1	8.7	11.4
Total	7.7	10.5	13.2

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