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Risk factors for gastric precancerous and cancers lesions in Latin American counties with difference gastric cancer risk

Lourdes Flores Luna¹, Maria Mercedes Bravo², Elena Kasamatsu³, Eduardo César Lazcano Ponce¹, Teresa Martinez⁴, Javier Torres⁵, Margarita Camorlinga-Ponce⁵, Ikuko Kato^{6,*}

¹Research Center in Health Population, National Institute of Public Health, Cuernavaca, Morelos, Mexico.

²Grupo de Investigación en Biología del Cáncer. Instituto Nacional de Cancerología, Bogotá, Colombia

³Research Institute in Health Sciences, National University of Asunción. Asuncion, Paraguay.

⁴Grupo de Investigación Epidemiológica del Cáncer. Instituto Nacional de Cancerología, Bogotá, Colombia

⁵Infectious Diseases Research Unit, CMNS-XXI, IMSS, Mexico City, Mexico

⁶Department of Oncology and Department of Pathology, Wayne State University School of Medicine, Detroit, USA

Abstract

Objective: To evaluate the risk factors associated with pre-neoplastic lesions and gastric cancer in countries with different cancer risk in Latin America.

Methods: 1222 questionnaires of risk factors related to pre-neoplastic lesions and gastric cancer were obtained from patients from Mexico (N=559), Colombia (N=461) and Paraguay (N=202), who were treated at the gastroenterology or oncology service of participant hospitals. In addition, biopsies specimens to establish histological diagnosis and blood to detect IgG antibodies against *Helicobacter-pylori* (*H. pylori*) whole-cell antigens and CagA protein using an ELISA were collected. These consisted of 205 gastric cancer, 379 pre-neoplastic (intestinal metaplasia (IM) /

*Corresponding Author: Ikuko Kato, katoi@karmanos.org, telephone 313-578-4206.

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Authorship statement

Conception, design and acquisition of data

Lourdes Flores Luna, Maria Mercedes Bravo, Elena Kasamatsu, Eduardo César Lazcano Ponce, Teresa Martinez, Javier Torres, Margarita Camorlinga-Ponce, Ikuko Kato

Analysis of data

Lourdes Flores Luna

Drafting and revising the article

Lourdes Flores Luna, Maria Mercedes Bravo, Elena Kasamatsu, Teresa Martinez, Javier Torres, Ikuko Kato

Conflict of interest

The authors declare no competing interests.

atrophic gastritis) and 638 control (normal /non-atrophic gastritis) cases. The odds ratio (OR) and 95% confidence intervals (CI) associated with potential risk factors were estimated by polynomial logistic regression model.

Results: Seropositivity to *H. pylori* was associated with risk of pre-neoplastic lesions, with OR = 1.9 (CI 95% 1.2–2.9; p=0.006) Grain / cereal intake (OR = 1.6, 95% CI 1.0–2.5; p=0.049) and egg intake (OR=1.7 95% CI 1.1–2.6; p=0.021) were related to gastric cancer. Among, people who did not developed gastric cancer, smoking more than five cigarettes per day had the highest risk of being infected by *H. pylori* (OR = 1.9; CI 95% 1.1–3.3; p=0.028).

Conclusion: The present study in Latin American countries confirmed that similar environmental factors such as smoking and grain/cereal consumption were associated with *H. pylori* infection and its induced gastric lesions as reported in other regions where dominant *H. pylori* strains differ.

Keywords

Risk factors; pre-neoplastic lesions; gastric cancer

Introduction

Gastric cancer remains the 3rd leading cause of cancer death and the leading cause of infection-related cancer worldwide and over 1,000,000 newly diagnosed cases and 783,000 deaths were estimated for year 2018 [1]. There are three recognized high risk regions worldwide, Eastern Asia, Central and Eastern Europe and Latin America. While there may be over-diagnoses in Eastern Asian countries [2], underreporting has been a concern for Latin American countries [3]. Interestingly, compared with the other high risk regions, Latin American countries show more pronounced geographical variations in gastric cancer incidence and mortality [4], even marked variations within countries [5]. Given comparably high prevalence rates of *Helicobacter pylori* (*H. pylori*), a major causative factor for gastric cancer, across Latin American countries [6], other environmental risk factors are likely to contribute to these variations.

Various environmental risk factors have been acknowledged to influence the risk of gastric cancer besides *Helicobacter* infection. These include socioeconomic status (SES) which is linked to housing and water treatment conditions, smoking, alcohol and dietary intake [7]. *H. pylori* infection has been documented to induce several stages of precancerous lesions, namely atrophic gastritis, intestinal metaplasia (IM) and dysplasia, leading to intestinal type of gastric adenocarcinoma [8,9] and some of the risk factors, such as SES, have been proposed to play the primary role in *H. pylori* acquisition [10] rather than in carcinogenesis itself. However, the roles of other environmental risk factors in the sequence of *H. pylori* associated precancerous and cancerous lesions have not been well depicted. Furthermore, although meta-analyses have detected significantly increased or decreased summary risk ratios for gastric cancer and several risk factors [11,12,7], these estimates often have accompanied by substantial heterogeneity among studies [11,12]. This suggests that the associations with some environmental risk factors are rather specific to certain local populations, probably due to food items only locally available or consumed, due to

heterogeneity of the inclusion criteria of individual food groups across studies [11] or due to different genetic background that may sensitize a person to certain environmental exposures [13].

In this paper, we summarize the associations of several environmental risk factors for gastric precancerous and cancerous lesions from a multicentric study conducted in 14 Latin American countries with different gastric cancer risk, Colombia, Mexico and Paraguay. The pathological diagnosis in each country was made by a single pathologist using centralized pathology review to standardize the criteria, the serologic assays were performed in a single reference laboratory in Mexico City, and standardized questionnaires were used to survey key risk factor information.

Materials and methods

Patients

The included patients from Mexico, Colombia and Paraguay are part of a multicentric study [14] originally organized by the International Agency for Research on Cancer (IARC). Sample size was based on the prevalence of type I *H. pylori* stain infection; however, other 17 initially invited countries could not participate in or complete the study and sample size was determined by feasibility and financial constraints. In Mexico, the patients (559) were recruited in the gastroenterology service of the General Hospital of Mexico “Dr. Eduardo Liceaga” and at the Siglo XXI Medical Center of the Mexican Institute of Social Security (IMSS), both in Mexico City; in Colombia the patients (461) came from the Hospitals of Tunja, and Barranquilla; and in Paraguay the patients (202) came from the Clinics Hospital and the General Hospital of the Social Provident Institute. The information was collected from October 1999 to July 2002, selecting patients aged 30 years and over who came to the hospital because they had gastroduodenal symptoms or due to probable gastric cancer, and who underwent an endoscopy and gastric biopsies. For the diagnosis and for the study, blood samples were also obtained. We excluded patients who had received previous treatment in the last two weeks with antibiotics, anti-inflammatory drugs, non-steroids, bismuth compounds and proton pump inhibitors, patients with esophageal varices, severe chronic diseases, and mental disorders and incapacitated. The Ethics Committee of each of the participating institutions approved the protocol. All patients signed the consent letter.

Questionnaires

The questionnaire applied to all the participants was designed and validated by the (IARC/WHO) and aimed to obtain information on the clinical, demographic characteristics, educational level, food consumption, smoking habits and drinking alcohol, salt consumption, use of refrigerator. Regarding food consumption, the number of portions consumed in a week was asked for each food, which was consolidated into eight groups for statistical analysis:

1. Potatoes
2. Vegetables: Raw green vegetables and salads, Cruciferae (broccoli, cabbage, Brussel sprout), Carrots, Fresh tomatoes (in season)

3. Grains: Bread, Pasta or rice, Maize dishes
4. Fruit: Fresh fruit juices, Apples or pears, Citrus fruit (oranges, grapefruit, lemons, kiwi), Bananas
5. Dairy: Milk, Yoghurt, Cheese
6. Egg
7. Meat/fish: Fresh meat, Fresh Fish, Preserved meat (ham, salami, sausages)
8. Leguminous: peas, beans, chickpeas, beans, etc.

Clinical diagnosis and blood samples.

Biopsies were taken from six predefined sites (two of lesser antrum curvature, one of greater antrum curvature, one of the angularis incisura, one of greater curvature of the body and one of the anterior face of the body) and from any visible tumor/lesion for histopathological studies and *H. pylori* detection for each patient. In each biopsy the presence of *H. pylori*, non-atrophic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia or gastric cancer was determined. The final diagnosis was the most severe histological lesion of all biopsies analyzed. *H. pylori* infection was considered histologically positive when the bacteria were observed in any of the six biopsies analyzed. A pathologist from each country reviewed biopsies after standardization of the criteria, and using consensus protocol Reading [14,15]. For this article, the final diagnosis was grouped into three: Normal/non-atrophic gastritis (Controls), Atrophic gastritis/ IM (Preneoplastic lesions), and Cancer/dysplasia (Gastric cancer). Five ml of serum was obtained from each patient, kept frozen at -20°C and analyzed for *H. pylori* serology.

ELISA for IgG anti- *Helicobacter pylori* and anti-CagA

All serologic assays were performed in a single reference laboratory in Mexico City under the direction of one of the authors (JT). Serum samples were divided into two aliquots and stored at -70°C until use. Serum samples from Colombia and Paraguay were shipped to Mexico on dry ice [16]. Immunoglobulin G (IgG) antibodies against *H. pylori* whole-cell antigens were tested in sera using an enzyme linked immunoabsorbent assay (ELISA), which was previously validated for Mexican population [17,18]. IgG antibodies against CagA were tested in sera using an ELISA previously validated. Patients were considered as seropositive for *H. pylori* infection when ELISA units were ≥ 1.0 . Cutoff for CagA seropositivity was defined as a value of ≥ 1.5 ELISA Units [17]. *H. pylori* seropositive was defined as patients who were *H. pylori* +/CagA +, *H. pylori* +/ CagA - or *H. pylori* -/ CagA +, and seronegative as patients with *H. pylori* -/ CagA-. This is because the serological response to CagA takes longer to disappear than the response to *H. pylori*. [19].

Statistical analysis

The analysis was based on the data of 1222 patients from Mexico, Paraguay and Colombia about whom complete information was available. Descriptive statistics, including the median, an interquartile range of 25–75, frequency and percentage, were used to describe the study population based on sociodemographic, diet, and clinical characteristics. The

relationship between characteristics of the patients and the presence of preneoplastic lesion and gastric cancer were estimated using multinomial logistic regression where reference category was control group (normal/non-atrophic gastritis). All models were adjusted for basic demographic variable, age, sex, education, length of refrigerator use, smoking status, country and serological *H. pylori* status. Trend tests were done to evaluate the increment or decrement between categories. This analysis was replicated by country with the variables that resulted in significant or close to significant associations in the previous analysis. In addition, a logistic regression was used to identify factors associated to *H. pylori* seropositivity in patients without cancer. Analyses were conducted using Stata software, version 14 (StataCorp LP, College Station, TX).

Results

A total of 1222 participants from Mexico, Colombia and Paraguay are included. Table 1 describes the types of pre-neoplastic lesions and gastric cancer; non-atrophic gastritis is more frequent in Mexico (65.8%), Atrophic gastritis / IM (43.4%) in Colombia and normal/non-atrophic gastritis (45.6%) in Paraguay. The infection by *H. pylori* and the age of the participants are similar in the three countries; participation of men (55.5%), smoking habits (50%), drinking alcohol (72.8%) and using refrigerator lifetime (50.5%) are more frequent in Paraguay, as well as adding salt to the meals (57.9%). The numbers of portions of potatoes, grain and leguminous are more frequent in Colombia and the consumption of vegetables, fruit, dairy, eggs and meat/fish are greater in Paraguay.

Tables 2, 3 and 4 show the results of the union of the three countries, according to the pre-neoplastic lesions and gastric cancer. Table 2 shows that the degree of education ($p>0.05$) and years using refrigerator ($p>0.05$) are not significant for pre-neoplastic lesions and gastric cancer. There is a significant relationship between *H. pylori* seropositivity and pre-neoplastic lesions (OR = 1.9, 95% CI, 1.2–2.9; $p=0.006$).

Table 3 shows that people who have taken alcohol, as well as those who have had more alcohol consumption, are not related to pre neoplastic lesions and gastric cancer. Nor is smoking related to pre neoplastic lesions (OR = 1.3, 95% CI 1.0–1.8; $p=0.094$) or smoking more than 5 cigarettes a day for gastric cancer (OR = 1.5, 95% CI 1.0–2.4; $p=0.073$).

Concerning the food groups (Table 4), it is observed that a higher consumption of potatoes, vegetables is not related to pre-neoplastic lesions or gastric cancer ($p>0.05$), whereas for grains/cereals the risk for gastric cancer increases as the tertile increases (OR = 6, 95% CI 1.0–2.5; $p=0.049$), showing a significant trend ($p=0.012$). Also, no relationship is observed for pre-neoplastic lesions and gastric cancer with the group of meat, dairy, fruits or legumes ($p>0.05$). Egg consumption shows a risk effect for gastric cancer when tertile three is compared against tertile one (OR = 1.7, 95% CI, 1.1 –2.6; $p=0.021$).

Next, we analyzed the major risk factors identified in Tables 3 and 4 separately for each country. Table 5 shows that smoking more than 5 cigarettes per day increased the risk particularly in Paraguay being significant for pre-neoplastic lesions. (OR = 3.1, 95% CI 1.0–9.5; $p=0.049$). Higher consumption (top tertile) of grains and cereals shows an increased

risk, being only significant for pre-neoplastic lesions in Colombia (OR = 2.2, 1.3–3.8; $p=0.002$). It is observed that higher egg consumption is a risk for gastric cancer in Colombia (OR = 3.2, 95% CI 1.5–7.0; $p=0.003$).

Table 6 among those who have not developed cancer shows a higher prevalence of *H. pylori* in the group of ever-smokers, and the risk of being infected by *H. pylori* is higher if they smoke more than 5 cigarettes / day OR = 1.9 (95% CI 1–3.3, $p=0.028$). Other factors were not associated with *H. pylori*-seropositivity (data not shown).

Discussion

There are several risk factors that have been linked to gastric cancer, such as salt intake, alcohol consumption and tobacco consumption [20,21]. In addition, infection with *H. pylori* is considered a risk factor for gastric cancer [22,23]. The study was conducted in three Latin American Countries, applying the same questionnaires to obtain information on the risk factors for pre-neoplastic lesions and gastric cancer, the information obtained from the three countries was analyzed jointly. To establish the final diagnosis of the patients, the pathologists from each country had a consensus meeting. Serological determinations of *H. pylori* were made by use of the same tests at a single institution [15,17,18]. The sero-prevalence of *H. pylori* was similar in the three countries (Mexico = 85.5%, Paraguay = 89.1% and Colombia = 87.4%), but higher than that reported by Flores-Luna et al (Mexico = 74.6%, Paraguay = 67.6% and Colombia = 72.4%) [16], based on the same study population. Although there was a small difference in the inclusion criteria for this analysis where we retained Colombian samples from low risk areas besides original samples from high risk areas, we consider that the observed differences in the prevalence from our previous estimates [16,14] were primarily due to the definition of sero-positivity. In this study, we incorporated CagA sero-positivity in addition to sero-positivity to anti-*H. pylori*, and thus subjects positive to either or both were classified to be *H. pylori*-seropositive.

The summary odds ratio in this study associated with *H. Pylori*-seropositivity for precancerous lesions (OR = 1.9, CI95% 1.2–2.9) was close to our previously reported estimate for Mexico (OR = 2.0, CI95% 1.1–3.4) [16,14] and that for gastric cancer (OR = 1.2, CI 95% 0.7–1.9) also coincided with the results of Flores -Luna et al and of Camorlinga-Ponce et al [16,14] as well as with the result of Cárdenas-Mondragon et al [24]. Weaker associations observed for gastric cancer in these studies may have been due to a disappearance of humoral *H. pylori* response as progression of the disease as reported by Camorlinga-Ponce M, et al [14] and Kokkola et al [25].

In this study, although the study population were all from Latin America, the three countries were different in gastric cancer risk and dietary and other environmental risk factors, as well as in health care systems. Therefore, in order to obtain comparable and translational results across the three countries we implemented the same selection criteria to select the study population and the same questionnaire to assess the risk factors. The final diagnosis of the patients was made by pathologists of each one who had a meeting of consensus, and the serological determinations of the three countries were carried out in the same laboratory, which gives validity to the results found. Yet, it was necessary to group the gastric lesions to

assess potential risk factors due to the limited numbers in certain diagnoses. Dysplasia could have been combined with either preneoplastic lesions (atrophic gastritis and IM) or gastric cancer. Because it was the smallest group representing only ~3%, and because most of the significant results were similarly observed in both preneoplastic and cancer groups, it is unlikely that grouping of dysplasia made a meaningful difference.

Besides *H. pylori*, cigarette smoking is the most consistently reported risk factor for gastric cancer, although the magnitude of the association is modest with the summary risk ratios less than 2.0 [7,12]. This association has also been replicated for premalignant lesions, especially for IM [26–29]. Overall, the results of the present study were consistent with those reported earlier by others, and the weaker association for premalignant lesions was likely due to lower intensity of smoking in these Latin American populations and use of combined group (IM plus atrophic gastritis) for a relatively small sample size. In addition to direct effect from tobacco-derived carcinogens [29], smoking and nicotine exert a myriad of pharmacological effect on gastrointestinal functions, leading to weaker mucosal defense against *H. pylori* [30]. Yet, it is rather unlikely that smoking plays a major role in *H. pylori* acquisition in high risk populations where the acquisition generally occurs in early childhood. However, growing evidence suggests that active smoking is an important risk factor for *H. pylori* eradication failure. The meta-analysis by Suzuki et al [31] summarized the data from various anti- *H. pylori* regimens, yielding the summary odds ratio of 1.95. A subsequent study in high risk Latin American population in Colombia replicated this results reporting the OR for eradication failure in smokers of 2.0 [29]. Since smoking and nicotine not only reduce mucosal blood flow thus drug delivery, but also antagonize proton pump inhibitors in reducing gastric acidity [30], the observed association is biologically plausible. In addition, decreased mucosal and systemic immune functions in smokers [30,32] may deter natural clearance of *H. pylori* in early stage of infection. These may explain our results indicating higher *H. pylori* seropositivity in smokers, compared with non-smokers, particularly those who smoked more than 5 cigarettes per day.

Earlier studies have reported inconsistent associations between grain/stable intake and the risk of gastric cancer or premalignant lesions. These foods are primary sources of starch and carbohydrate and not only encompass diverse food items, but also may be population-specific [11]. Moreover, some staples, such as potatoes and corns, are often analyzed as vegetable in other populations. Recent meta-analyses concerning total grains/cereals and carbohydrate intake failed to show a significant association with gastric cancer [11,33]. However, the latter meta-analysis on carbohydrate indicated that an increased risk was limited to Asians who were higher risk for gastric cancer [33]. Similarly, other studies conducted in high risk Latin American populations have pointed to increased risk of gastric cancer or precursor lesions with certain starchy foods; e.g., rice with gastric cancer in Uruguay [34] and atrophic gastritis in Brazil [35], starry vegetables with gastric cancer and precursor lesions in Venezuela [36,26] and corn with premalignant lesion in Colombia [37]. These results are consistent with the findings from the present study and may be generalized into low risk Latin American counties, such as Mexico. In fact, Denova-Gutierrez et al suggested that a dietary pattern represented by high refined grain intake was associated with gastric cancer risk in Mexico [38]. Because the association were rather consistent through precancerous lesions to gastric cancer and because there was no association with *H. pylori*

infection itself (data not shown), we would speculate that high starch diet may foster the development of premalignant lesions, if the association is causal. Despite these observations, however, there have been no plausible biological mechanisms substantiated, except a remote possibility of contamination of local grown grains, such as corns, by toxins or carcinogens [39]. Instead, high starch intake is more likely to represent traditional local diet, which lacks food variety and nutritional balance, especially in potentially beneficial nutrients such as vitamins and protein [34,36,26].

Likewise, the association between gastric cancer and animal food consumption has been inconclusive. Our study found only a positive association with egg, which was more pronounced for cancer than pre-neoplastic lesions. Meta-analyses have indicated no overall risk associated with total meat or total dairy intake for gastric cancer [11,40], while some including those from Latin American countries, suggested an increased risk associated with red or processed meat [11,12]. Much fewer studies have reported the results on egg consumptions, and the meta-analysis of six studies has shown a null effect (RR=1.06). Two ecological studies in high risk countries, China and Brazil, have reported geographical positive correlations between gastric cancer mortality and egg consumption at the population level [41,42]. When IM was used as an outcome, the cases reported higher intake of eggs than the controls [43]. Interestingly, promoter hypermethylation of a putative tumor suppressor, *RUNX3*, which silences gene expression, was found more frequently in patients consuming more eggs than in those with lower egg consumption [44]. Moreover, *RUNX3* hypermethylation has been reported to increase stepwise through atrophic gastritis, IM to dysplasia [45], which corroborates the strengths of the associations found in this study for pre-neoplastic lesions and cancer. Finally, Ikezaki et al reported that higher intakes of egg and cholesterol led to lower eradication of *H. pylori* by anti-*H. pylori* treatment [46], interpreting that cholesterol from eggs can augment *H. pylori* virulence through the biosynthesis of cholesterol-a-glucosides by *H. pylori* themselves [47]. Although we did not find any association between egg intake and *H. pylori*-seropositivity among non-cancer patients, serology has a limitation in assessing actual presence of *H. pylori* in gastric mucosa.

In summary, the present study conducted in Latin American populations, where prevalence of *H. pylori* remains high particularly in adults [48] and long-term exposure to *H. pylori* is associated with progression of premalignant lesions [49] and found the associations between high starch diet, egg intake with gastric cancer risk and that between cigarette smoking and *H. pylori* seropositivity. The results were generally consistent with those from other high-risk countries. Further studies are warranted to delineate how these environmental factors possibly pry oncogenic pathways activated by various *H. pylori* virulence factors.

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Highlights

- Gastric cancer remains the leading cause of infection-related cancer in 2018.
- 1222 patients with various gastric pathology were recruited in Latin American
- Seropositivity to *H. pylori* was associated with risk of pre-neoplastic lesions.
- Grain/cereal intake and egg intake were related to gastric cancer.
- Cigarette smoking was associated with risk of being infected by *H. pylori*.

Table 1.

Characteristics of patients from Mexico, Paraguay and Colombia

Characteristics	Mexico n=559	Paraguay n=202	Colombia n=461
Normal/non-atrophic gastritis (N,%)	368 (65.8)	92 (45.6)	178 (38.6)
Atrophic gastritis/ IM (N,%)	124 (22.2)	55 (27.2)	200 (43.4)
Cancer/dysplasia (N,%)	67 (12.0)	55 (27.2)	83 (18.0)
HP serology + (%)	85.5	89.1	87.4
Sex : male (%)	42.9	55.5	49.9
Age (median, tertile range)	50 (40–62)	54 (42–65)	53 (42–64)
Secondary school + (%)	34	28.2	38.6
Lifetime fridge use (%)	15.4	50.5	39.7
Ever smoker (%)	42	50	38.2
Ever alcohol use (%)	39.9	72.8	66.6
Table salt use (%)	43.8	57.9	37.5
Potatoes (median, tertile range)	2 (1–3)	6 (3–7)	14 (4–42)
Grain (median, tertile range)	10 (6–14)	15 (12–22)	17 (14–23)
Vegetables (median, tertile range)	7 (4–11)	13 (8–19)	8 (2–14)
Fruit (median, tertile range)	7 (3–12)	13 (8–18)	11 (4–16)
Dairy (median, tertile range)	7 (2–12)	11 (8–18)	6 (2–10)
Egg (median, tertile range)	2 (1–4)	3 (1–4)	2 (1–4)
Meat/fish (median, tertile range)	4 (2–7)	7 (6–10)	5 (2–8)
Leguminous (median, tertile range)	3 (2–6)	1 (0–2)	4 (2–7)

Table 2.

Association between demographic characteristics, *Helicobacter pylori* seropositivity and risk of pre-neoplastic lesions and gastric cancer in patients from Mexico, Paraguay and Colombia

Variables	Controls n= 638		Preneoplastic lesion n= 379			Gastric cancer n=205			
	No.	No.	OR	P value	95% CI	No.	OR	P Value	95% CI
Years of education									
None	68	63	1			43	1		
Primary	292	207	1.1	0.645	0.7–1.7	123	0.9	0.714	0.5–1.5
Secondary and University	277	108	0.9	0.677	0.5–1.5	39	0.6	0.121	0.3–1.1
Length of refrigerator use									
0–9 years	228	159	1			80	1		
10–29 years	144	74	1	0.976	0.7–1.5	37	0.8	0.369	0.5–1.3
30+ years	264	140	0.7	0.131	0.5–1.1	86	0.8	0.414	0.5–1.3
Add salt to meals									
Never	352	228	1			106	1		
Sometimes	162	97	0.9	0.788	0.7–1.3	51	0.8	0.283	0.5–1.2
Almost always and always	123	53	0.7	0.060	0.5–1.0	48	1.1	0.753	0.7–1.7
Serological status									
<i>H. pylori</i> (-) Cag A (-)	96	35	1			30	1		
<i>H. pylori</i> (+, -) or Cag A(+,-)	542	344	1.9	0.006	1.2–2.9	175	1.2	0.508	0.7–1.9

Note: ORs are adjusted for basic demographic variable, age, sex, educational level, length of refrigerator use, country and serological status to *Helicobacter pylori*

Table 3.

Association between smoking habits, alcohol consumption and risk of pre-neoplastic lesions and gastric cancer in patients from Mexico, Paraguay and Colombia

Variables	No. Controls n= 638		Preneoplastic lesion n= 379			Gastric cancer n=205			
	No.	No.	OR	P value	95% CI	No.	OR	P value	95% CI
Drinking alcohol									
Never drinking alcohol	325	153	1			67	1		
Ever drinking alcohol	313	226	1.1	0.728	0.8–1.5	138	1.0	0.846	0.7–1.6
Alcohol status									
Never	325	153	1			67	1		
Ex-consumer	146	127	1.2	0.333	0.8–1.8	99	1.3	0.212	0.8–2.1
Current consumer	167	99	0.9	0.696	0.6–1.4	39	0.7	0.156	0.4–1.2
Alcohol amount									
Never	325	153	1			67	1		
Median	150	88	1.0	0.949	0.7–1.5	51	1.0	0.951	0.6–1.7
>Median	149	123	1.1	0.580	0.7–1.7	83	1.1	0.703	0.7–1.8
Smoking									
Never smoking	394	217	1			99	1		
Ever smoking	244	162	1.3	0.094	1.0–1.8	106	1.3	0.148	0.9–2.0
Smoking status									
Never	394	217	1			99	1		
Ex-consumer	144	109	1.3	0.195	0.9–1.8	82	1.4	0.093	0.9–2.2
Current consumer	100	53	1.4	0.128	0.9–2.1	24	1.1	0.781	0.6–1.9
Smoking amount									
Never	394	217	1			99	1		
≤5/day	131	75	1.2	0.191	0.9–1.9	39	1.1	0.581	0.7–1.9
>5 /day	113	86	1.3	0.156	0.9–2.0	67	1.5	0.073	1.0–2.4

Note: ORs are adjusted for basic demographic variable, age, sex, educational level, length of refrigerator use, country and serological status to *Helicobacter pylori*

Table 4.

Association between food consumption (in tertiles) and risk of pre-neoplastic lesions and gastric cancer in patients from Mexico, Paraguay and Colombia

Food groups Tertile	No. Controls n= 638	Preneoplastic lesion n= 379				Gastric cancer n=205				
		No.	No.	OR	P value	95% CI	No.	OR	P Value	95% CI
Potatoes										
1	266	106	1				62	1		
2	203	133	1.2	0.166	0.9–1.8		75	1.0	0.944	0.6–1.6
3	168	139	1.3	0.135	0.9–1.9		68	1.3	0.328	0.8–2.0
P value trend			0.267					0.250		
Vegetables										
1	222	136	1				85	1		
2	232	135	1.2	0.316	0.8–1.7		66	1.0	0.955	0.7–1.5
3	183	106	1.2	0.409	0.8–1.7		54	1.1	0.702	0.7–1.7
P value trend			0.578					0.780		
Grain/cereals										
1	236	123	1				58	1		
2	230	102	0.9	0.709	0.6–1.3		72	1.4	0.146	0.9–2.1
3	171	153	1.5	0.030	1.03–2.0		75	1.6	0.049	1.0–2.5
P value trend			0.056					0.012		
Meat/fish										
1	251	201	1				103	1		
2	197	85	0.6	0.018	0.5–0.9		44	0.8	0.452	0.5–1.3
3	188	92	0.8	0.161	0.5–1.1		58	1.1	0.560	0.7–1.8
P value trend			0.211					0.584		
Dairy										
1	217	151	1				66	1		
2	223	117	0.8	0.322	0.6–1.2		82	1.4	0.089	0.9–2.2
3	197	110	1.1	0.771	0.7–1.5		57	1.4	0.155	0.9–2.3
P value trend			0.807					0.242		
Fruit										
1	220	152	1				73	1		
2	219	144	1.2	0.270	0.9–1.7		75	1.5	0.077	0.9–2.3
3	198	102	0.9	0.971	0.7–1.4		57	1.3	0.260	0.8–2.1
P value trend			0.935					0.637		
Egg										
1	296	158	1				82	1		
2	194	122	0.8	0.345	0.6–1.2		52	0.7	0.218	0.5–1.2
3	147	98	1.2	0.319	0.8–1.7		71	1.7	0.021	1.1–2.6
P value trend			0.192					0.029		
Leguminous										

Food groups Tertile	No. Controls n= 638	Preneoplastic lesion n= 379				Gastric cancer n=205			
		No.	No.	OR	P value	95% CI	No.	OR	P Value
1	249	142	1			64	1		
2	203	97	0.7	0.086	0.5–1.0	70	0.9	0.696	0.6–1.4
3	194	138	0.9	0.520	0.6–1.2	70	1.0	0.954	0.6–1.5
P value trend			0.904				0.897		

Note: ORs are adjusted for basic demographic variable, age, sex, educational level, length of refrigerator use, smoking status, country and serological status to *Helicobacter pylori*

Table 5.

Association between smoking habits, food consumption and risk of pre-neoplastic lesions and gastric cancer in Mexico, Paraguay and Colombia.

México (N=559)										Paraguay (N=202)				Colombia (N=461)			
No.	No.	OR	P value	95%CI	No.	Controls	Preneoplastic lesion	OR	P value	95%CI	No.	Controls	Preneoplastic lesion	OR	P value	95%CI	
Smoking amount	Controls																
Never	222	74	1		57	22	1				115	121	1				
<=5/day	76	28	1.7	0.089	0.9–2.9	20	13	1.8	0.248	0.7–4.6	35	34	0.9	0.809	0.5–1.7		
>5 /day	70	22	1.2	0.526	0.7–2.3	15	20	3.1	0.049	1.0–9.5	28	44	1.2	0.560	0.6–1.3		
P value trend			0.596					0.069						0.517			
Never	222	28	1		57	22	1				115	49	1				
<= 5 /day	76	19	2.1	0.054	1.0–4.3	20	15	1.8	0.268	0.6–5.1	35	5	0.4	0.061	0.1–1.0		
>5 /day	70	20	1.8	0.118	0.9–3.8	15	18	1.4	0.601	0.4–4.3	28	29	1.6	0.221	0.7–3.5		
P value trend			0.423					0.971						0.120			
Grain/cereals	Controls																
Tertile 1	129	50	1		32	19	1				75	54	1				
Tertile 2	154	48	0.8	0.613	0.5–1.4	31	16	1.3	0.570	0.5–3.3	45	38	1.1	0.697	0.6–2.0		
Tertile 3	85	26	1	0.996	0.5–1.9	29	20	1.4	0.440	0.6–3.7	57	107	2.2	0.002	1.3–3.8		
P value trend			0.929					0.388						0.003			
Tertile 1	129	19	1		32	18	1				75	21	1				
Tertile 2	154	30	1.3	0.443	0.6–2.5	31	14	1.4	0.506	0.5–4.3	45	28	1.6	0.248	0.7–3.4		
Tertile 3	85	18	1.8	0.154	0.8–3.9	29	23	1.6	0.348	0.6–4.7	57	34	1.3	0.449	0.6–2.8		
P value trend			0.138					0.193						0.311			
Egg	Controls																
Tertile 1	185	61	1		42	31	1				69	66	1				
Tertile 2	88	32	1	0.852	0.6–1.8	30	10	0.5	0.122	0.2–1.2	76	80	1	0.957	0.6–1.7		
Tertile 3	95	31	1.2	0.444	0.7–2.1	20	14	1.1	0.811	0.4–2.8	32	53	1.8	0.064	1.0–3.2		
P value trend			0.334					0.912						0.076			

	México (N=559)					Paraguay (N=202)					Colombia (N=461)				
	No.	No.	OR	P value	95%CI	No.	OR	P value	95%CI	No.	OR	P value	95%CI		
Gastric cancer															
Tertile 1	185	39	1			42	19	1		69	24	1			
Tertile 2	88	8	0.3	0.012	0.1–0.8	30	20	1.7	0.283	76	24	0.8	0.612	0.4–1.7	
Tertile 3	95	20	1	0.890	0.5–2.0	20	16	1.9	0.214	32	35	3.2	0.003	1.5–7.0	
P value trend			0.796					0.235				0.002			

Note: ORs are adjusted for basic demographic variable, age, sex, educational level, length of refrigerator use, smoking status and serological status to *Helicobacter pylori*

Table 6.

Association of smoking habits and risk of seropositivity to *Helicobacter pylori* in patients without cancer from Mexico, Paraguay and Colombia

Variable	<i>Helicobacter pylori</i>			
	Negative n=131(%)	Positive n= 886 (%)	OR	P value 95% CI
Smoking				
Never smoking	86 (65.7)	525 (59.3)	1	
Ever smoking	45 (34.3)	361 (40.7)	1.5	1.0–2.2
Smoking status				
Never	86 (65.7)	525 (59.3)	1	
Ex-consumer	29 (22.1)	224 (25.3)	1.4	0.8–2.2
Current consumer	16 (12.2)	137 (15.4)	1.6	0.9–2.9
Smoking amount				
Never	86 (65.7)	525 (59.3)	1	
<= 5/day	27 (20.6)	179 (20.2)	1.2	0.460 0.7–1.9
>5 /day	18 (13.7)	181 (20.5)	1.9	0.028 1.1–3.3

Note: ORs are adjusted for basic demographic variablese. age, sex, educational level, length of refrigerator use and country