Prevalence of Precancerous Lesions of the Stomach in Venezuela[1]

Nubia Muñoz,[2] Ikuko Kato, Simon Peraza, Gladys Lopez, Elsa Carrillo, Hernan Ramirez, Jorge Vivas, Denis Castro, Victor Sanchez, Olga Andrade, Eva Buiatti, and Walter Oliver

Unit of Field and Intervention Studies, International Agency for Research on Cancer, 150 Cours Albert-Thomas, 69372 Lyon, Cedex 08 France [I. K., N. M.]; Cancer Control Center of the Tachira State, San Cristobal, 5050 Venezuela [S. P., G. L., E. C., D. C., V. S., O. A., J. V., W. O.]; Universidad de Valle, Cali, Colombia [H. R.]; and Epidemiology Unit, Centro per lo Studio e la Prevenzione Oncologica, I 50135, Florence, Italy [E. B.]

Abstract

Gastric biopsies from 1477 participants in a chemoprevention trial for precancerous lesions of the stomach in Venezuela were evaluated for the prevalence of precancerous lesions and *Helicobacter pylori* infection. These study subjects were selected from participants in an early detection program for gastric cancer using double-contrast X-ray. Overall, 94% had some type of chronic gastritis (CG) and were positive for *H. pylori* using Giemsa stain, 49% had atrophic gastritis, 34% had intestinal metaplasia (IM), and 6.5% had dysplasia. There were only three subjects (0.2%) with normal gastric mucosa, and 4% had only superficial gastritis. The prevalence of all of these precancerous lesions increased with age, but there was no clear difference by gender. The prevalence of the various lesions was higher in the antral mucosa than in the fundic mucosa. *H. pylori* infection was strikingly frequent in our study population, with prevalence rates ranging from 73% in subjects with superficial gastritis to 95% in those with atrophic gastritis and IM and 98% in those with CG. The prevalence of *H. pylori* was equally high in males and females, and it was significantly positively associated with the degree of infiltration of poly- and mononuclear cells and with that of active regeneration; it was inversely correlated with the degree of atrophy, IM, and dysplasia. Our findings support the precancerous nature of the various gastric lesions and the etiological role of *H. pylori* infection in CG.

Introduction

There are two main types of stomach cancer, the intestinal and the diffuse. The intestinal type is considered epidemic and accounts for the excess incidence in high-risk populations, suggesting a larger role for environmental factors in its etiology (1). However, the few case-control studies by histological type reported thus far indicate dietary risk factors that are common for the two histological types (2). Several stages of premalignant lesions that represent a continuum of changes from normal to carcinoma have been proposed for the intestinal type of stomach cancer. These include SG,[3] CG, AG, IM, and dysplasia, in order of increasing severity (3). The complete process has been estimated to take at least a few decades (4).

Helicobacter pylori, a gram-negative spiral bacterium that has adapted to the environment of the human stomach, has been implicated in various gastro-duodenal conditions and has also been associated with gastric cancer (5–7). *Helicobacter pylori* infection may play a central role in the early stages of the chain of events leading to gastric cancer. Inflammation increases cell proliferation, thus increasing the risk of DNA damage, and the production of reactive oxygen species by activated polynuclear leukocytes at its turn may also cause DNA damage. In a long-term follow-up study the development of SG was associated with the presence or persistence of *H. pylori* infection, but the further progression into CG was related less clearly to infection with this bacterium (8), suggesting the importance of *H. pylori* infection in the first stages of pathogenesis of gastric precursor lesions.

Earlier studies have described the prevalence of precancerous lesions in selected populations (9). In the Andean region of Venezuela, stomach cancer is the leading cause of death from cancer, and the Andean region of Latin America is one of the highest risk areas in the world (10). Nevertheless, there are very scanty data on the prevalence of precancerous lesions of the stomach and of *H. pylori* infection in this population. The results reported here are based on the baseline examination of the subjects recruited in an on-going chemoprevention trial for stomach cancer in Venezuela.

Materials and Methods

The main purpose of the double-blind chemoprevention trial is to assess the effect of antioxidant vitamins on the progression of gastric precancerous lesions. The study population is derived from the participants in the Gastric Cancer Control Program of Tachira state (Tachira, Venezuela) which has the aim of early detection of gastric cancer, using double contrast X-ray, followed by a gastroscopic examination when abnormalities of the gastric wall are detected. These include irregular, granular, or convergent mucosal folds and filling defects. Among the participants undergoing a gastroscopic examination after X-ray, eligible subjects are permanent residents of the state of Tachira between the ages of 35 and 69 years, in general good health, and who give their consent to participate in the prevention trial. At entry into the trial, an interview to elicit information on risk factors for stomach cancer, a physical examination, blood collection, and gastroscopy were performed.

At gastroscopy seven biopsies from standardized sites of

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[1] This study was supported by European Community Contract CT90-0555.
[2] To whom request for reprints should be addressed. Phone: (33) 72.73.84.02.

[3] The abbreviations used are: SG, superficial gastritis; CG, chronic gastritis; AG, atrophic gastritis; IM, intestinal metaplasia.

Table 1 Distribution of number of gastric biopsies by area of the stomach

No. of biopsies	Whole stomach		Fundus		Antrum	
	n	%	*n*	%	*n*	%
0	0	0.0	604	40.9	4	0.3
1	1	0.1	833	56.4	13	0.9
2	4	0.3	37	2.5	65	4.4
3	15	1.0	2	0.1	250	16.9
4	84	5.7	0	0.0	805	54.5
5	1373	93.0	1	0.1	340	23.0
Total	1477	100.0	1477	100.0	1477	100.0

the stomach are being taken, two of which are frozen and five of which are processed for histopathological evaluation. The five biopsies for histological assessment are taken from the lesser curvature of the antrum (approximately 1 cm from the pylorus), from the greater curvature of the antrum (approximately 1 cm above the pylorus), from a mid-portion of the lesser curvature of the antrum, from the lesser curvature of the antrum immediately below the incisura, and from the middle corpus (approximately 2 cm from the lesser curvature). The samples to be stored frozen are taken from the greater curvature of the antrum, approximately 1–2 cm below the antrum corpus junction, and from a middle portion of the anterior wall of the antrum.

All gastric biopsies (except for the two frozen) were fixed in buffered formalin and stained with hematoxylin-eosin and Giemsa to detect *H. pylori*. Those biopsies positive for IM were also stained with PAS Alcian Blue and HID-Alcian Blue to determine subtypes of IM. All slides were read by three pathologists at the pathology laboratory of the Cancer Control Center after training sessions with consultant pathologists (Drs. P. Correa, H. Ramirez, and I. Filipe) with great experience in gastric pathology. Because interobserver variation tended to be higher for the diagnosis of dysplasia (the local pathologists had a tendency to over diagnose dysplasia), all slides with dysplasia were reviewed by two consultant pathologists (H.R. and J.T.), and their diagnoses were used for the analyses. For each biopsy, the following variables were recorded in a standard form: type and depth of mucosa biopsied, degrees of neutrophil and mononuclear infiltration, active regeneration, glandular atrophy, IM and dysplasia, depth of inflammatory infiltration, presence and type of IM, and quantity of *H. pylori* infection (0, none; 1, difficult to find; 2, easy to find; and 3, abundant). Most of these lesions (except for depth of infiltration and type of IM) were graded as none, mild, moderate, or severe and scored as 0–3, respectively. The fundic mucosa was confirmed by the presence of oxyntic cells. The diagnoses for SG, CA, AG, IM, and dysplasia were defined as follows.

SG is characterized by infiltration of mononuclear and polymorphonuclear leukocytes in the superficial portion of the lamina propria and by focal necrosis and regenerative changes in the glandular neck region.

In CG lymphoplasmocytic cells infiltrate deeper layers of the mucosa.

Chronic AG is characterized by loss of normal glands, which are partly replaced by connective tissue and inflammatory cells.

In IM the gastric glands are replaced by cells normally present only in the intestine, absorptive, goblet, argentaffin, and Paneth cells. IM subtypes were classified according to Filipe and Jass (11) as follows:

Type I. Straight crypts are lined by mature goblet and absorptive cells with a well defined brush border. Paneth cells are often present at the crypt base. Goblet cells secrete sialomucins and occasionally sulfomucin, and absorptive cells are nonsecretory.

Type II. There is mild architectural distortion, crypts are lined by goblet cells, absorptive cells are few or absent, and columnar mucous cells are present in variable number and stage of differentiation. The columnar cells contain a mixture of neutral and acid sialomucins, and goblet cells secrete sialomucins or occasionally sulfomucins, or both. Paneth cells are inconspicuous or absent.

Type III. The crypts are tortuous and branched at their base, and the overall architecture is more disorganized than in type II. The ratio of immature columnar cells to goblet cells is increased. Columnar cells secrete sulfomucins, and goblet cells contain sialo- or sulfomucins. Paneth cells are not common.

Dysplasia is characterized by closely packed tubular glands with diminished mucus secretion, scant cytoplasm, and large, hyperchromatic, crowded, and elongated nuclei.

Diagnosis for each lesion was independent except for those of SG and CG, which were mutually exclusive. All positive diagnoses in any biopsy were considered for the overall prevalence, but the most severe lesion among all biopsies was considered for the global diagnosis. A global diagnosis "normal" applied when none of the above-listed lesions was detected in any biopsy.

The overall prevalence of CG, AG, IM, and dysplasia and the distribution of the global histological diagnosis were calculated by age and sex, and the prevalence of *H. pylori* infection was estimated by the global histological diagnosis and by age. The association between degrees of *H. pylori* infection and of other pathological conditions was examined among all gastric biopsies evaluable by calculating mean *H. pylori* scores by the degree of other pathological conditions and by estimating the correlation coefficients between them.

Results

A total of 1477 participants who were enrolled in the chemoprevention trial between January 1991 and December 1993 were included in this analysis. During this time period a total of 19,537 subjects underwent X-ray examination, and 7,970 of them had gastroscopy performed. Of those undergoing gastroscopy, 3053 fulfilled the inclusion criteria and 1505 of them were invited to participate in the trial. All five gastric biopsies for histological evaluation were successfully taken in 93% of the subjects, and nearly 99% subjects had four or more gastric biopsies taken. However, gastric biopsy from the fundic mucosa was successful for only 59% of the subjects (Table 1).

Table 2 Sex- and age-specific overall prevalence rates (percentage) of precancerous lesions in Venezuela. All the available biopsies of each subject are considered for diagnosis

Sex/age (yr)	No. of subjects	CG	AG	IM subtypes				Dysplasia
				All	I	II	III	
Male								
35–39	166	91.6	34.3	22.3	18.1	4.8	3.6	3.6
40–49	246	94.7	42.3	30.5	26.8	7.3	5.3	7.7
50–59	186	96.2	58.7	45.2	37.6	14.5	9.7	5.9
60–69	95	95.8	65.3	51.6	43.2	20.0	11.6	13.7
Total	693	94.5	47.9	35.4	29.9	10.4	6.9	7.1
Female								
35–39	177	92.1	38.6	20.3	17.0	5.7	4.5	3.4
40–49	273	92.3	45.0	27.8	24.9	6.6	5.5	5.1
50–59	206	94.2	55.0	36.9	31.6	12.1	11.2	6.3
60–69	128	93.0	64.3	52.3	43.8	21.1	14.8	10.9
Total	784	92.9	49.7	32.5	27.9	10.2	8.3	6.0

Table 3 Distribution (percentage) of the global diagnosis of precancerous lesions by sex and age

Sex/age (yr)	No. of subjects	Normal/SG	CG	AG	IM subtypes				Dysplasia
					All	I	II	III	
Male									
35–39	166	7.2	54.8	15.7	18.7	14.5	2.4	1.8	3.6
40–49	246	3.7	46.8	17.1	24.8	19.1	3.3	2.4	7.7
50–59	186	2.2	34.4	18.3	39.2	24.2	8.6	6.5	5.9
60–69	95	3.2	27.4	17.9	37.9	25.3	10.5	2.1	13.7
Total	693	4.0	42.7	17.2	29.0	20.2	5.5	3.3	7.1
Female									
35–39	177	5.1	53.1	20.9	17.5	12.4	2.3	2.8	3.4
40–49	273	5.1	46.2	20.5	23.1	18.0	2.2	2.9	5.1
50–59	206	3.4	37.9	21.8	30.6	21.4	3.4	5.8	6.3
60–69	128	3.9	28.1	15.6	41.4	21.9	11.7	7.8	10.9
Total	784	4.5	42.6	20.2	26.8	18.2	4.1	4.5	6.0

The overall prevalences of the various lesions were: 94% for CG, 49% for AG, 34% for IM, (29% type I, 10% type II, and 8% type III), and 6.5% for dysplasia. The prevalence of all these precancerous lesions tended to increase with age. There was no clear gender difference in the prevalence of any lesion, although IM and dysplasia were slightly more frequent in males (Table 2).

Table 3 shows the distribution by age and sex of the global diagnosis. Because there were only three subjects (0.2%) with normal gastric mucosa, they were combined with those with SG. CG was the most common in both males and females, followed by IM, AG, and dysplasia. The proportions of the global diagnosis of IM and dysplasia increased with age, whereas those of CG and normal plus SG decreased with age and AG showed no relation with age.

The overall prevalence of each lesion was much lower on the fundic mucosa compared to the antral mucosa. The prevalence of lesions in the antral mucosa was almost identical to that based on all biopsies (Table 4).

Figs. 1 and 2 show the distribution of the number of biopsy sites found to be positive in subjects with CG and AG and in those with IM and dysplasia, respectively. For 61% of those with dysplasia, the diagnosis was based on one positive biopsy and for 29% of them, on two positive biopsies. AG and IM were diagnosed in 62 and 78% of the cases, respectively, in one or two biopsies, whereas 80% of those with CG showed this lesion in three or more biopsies.

Ninety-four % of the study population was positive for *H. pylori*. There was no gender difference in the prevalence of *H. pylori*. The prevalence of *H. pylori* infection was high in all lesions, but it was highest for the global diagnoses of CG (97.5%), followed by IM (95.4%) and AG (95.0%) and lower for the global diagnoses of dysplasia (85.4%) and SG plus normal (73.0%). There was no clear trend with age for the *H. pylori* prevalence in any lesion (Table 5).

As shown in Table 6, the *H. pylori* score was significantly positively associated with the degree of infiltration of polynuclear cells and monocytes and with that of active regeneration, and it was inversely correlated with the degree of atrophy, IM, and dysplasia.

Discussion

The present study ascertained for the first time the very high prevalence of gastric precancerous lesions in a Venezuelan population at high risk for stomach cancer.

Some caution should be exercised in interpreting these data and in comparing them with the results from other studies. First, our study population is not necessarily representative of the general population in Venezuela. About 40% of the subjects

Table 4 Age-specific overall prevalence rates (percentage) of precancerous lesions by type of gastric mucosa (both sexes combined)

Type of mucosa/ age (yr)	No. of subjects	CG	AG	IM subtypes				Dysplasia
				All	I	II	III	
Fundic								
35–39	215	31.6	3.9	3.3	2.3	0.9	0.0	0.5
40–49	312	33.3	5.2	3.8	2.2	1.6	0.3	1.0
50–59	223	35.6	9.7	3.2	2.2	0.9	0.9	0.5
60–69	123	36.9	9.3	4.1	0.8	3.3	0.0	0.8
Total	873	34.0	6.6	3.6	2.1	1.5	0.3	0.7
Antral								
35–39	342	91.8	36.1	18.7	17.0	5.7	4.5	2.9
40–49	516	92.8	43.5	27.1	24.9	6.6	5.5	5.6
50–59	392	94.4	56.8	38.0	31.6	12.1	11.2	4.9
60–69	223	92.4	64.1	49.3	43.8	21.1	14.8	9.4
Total	1473	92.9	43.4	31.4	27.9	10.2	8.3	5.4

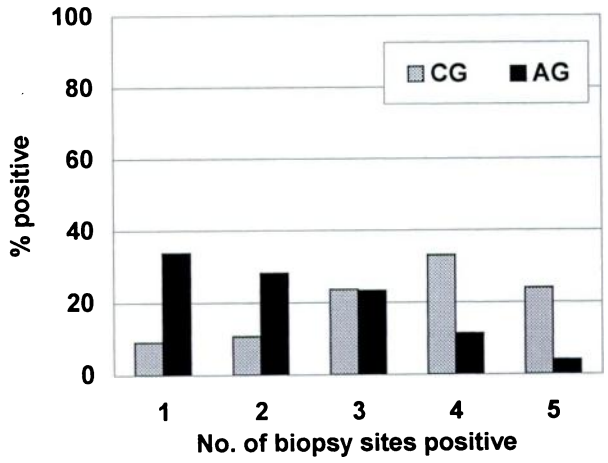

Fig. 1. Percentage distributions of the number of biopsy sites with CG and AG by global diagnosis.

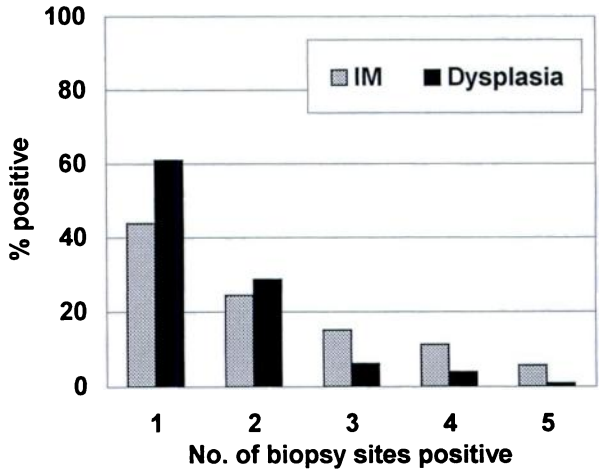

Fig. 2. Percentage distributions of the number of biopsy sites with IM and dysplasia by global diagnosis.

who participated in a stomach cancer screening program were selected for gastroscopy because they had radiological alterations of the gastric mucosa. About 40% of those undergoing endoscopy fulfilled the inclusion criteria to enter into the chemoprevention trial, and 98% of those invited to participate accepted to be enrolled into the trial. Gastric symptoms, mainly mild dyspepsia, represent a possible reason for participating in this screening; additionally, 95% of those who have been enrolled in the chemoprevention trial reported living in urban areas. Although the first of these selections is expected to lead to overestimation of gastric lesions, the second should play the opposite role. However, it should be noted that the selected nature of the study population is common to most studies in which prevalence of gastric lesions is determined through endoscopy and biopsy.

In comparing our results with the prevalence rates obtained in other studies, some other points should be kept in mind. The number of biopsies taken may influence the prevalence estimates. In this study, five biopsies were taken from a large majority of subjects according to a standardized protocol, and only 20 of 1477 (1.5%) had less than four biopsies. This should ensure a good representation of the gastric mucosa. In addition, when results from more than one pathologist are compared, interobserver variation may affect the prevalence estimate. Our preliminary pathological reviews for quality control indicate that this variation may be high for dysplasia, whereas reproducibility is good for IM. The three pathologists involved in the present study frequently compared their diagnoses through peer review of slides. Furthermore, all dysplasias first identified were reevaluated by two independent pathologists. However, possible differences between their diagnostic criteria and those in other studies should be kept in mind when results are compared.

Despite these limitations, comparison of the present results with those from other studies reveals a pattern that is quite consistent with geographical differences in gastric cancer risk. Table 7 lists the prevalences of AG, IM, and dysplasia diagnosed by gastric biopsy in earlier studies involving subjects with a similar age range and compares them with the results in Venezuela (3, 12–18). Generally, high prevalences are observed in high-risk geographical areas for stomach cancer, such as Japan (12), China (13), and Colombia (3). It is interesting that the prevalence of the various precancerous lesions in the Venezuelan population, with the exception of dysplasia, which is somewhat lower, shows a similar pattern to that observed in

Table 5 Prevalence (percentage) of *H. pylori*-positive subjects by global diagnosis and age (both sexes combined)

Age (yr)	Normal/SG	CG	AG	IM subtypes				Dysplasia
				All	I	II	III	
35–39	71.4	98.4	93.7	95.2	93.5	100.0	100.0	83.3
40–49	82.6	97.1	94.9	98.4	97.9	100.0	100.0	93.9
50–59	54.6	96.5	94.9	93.4	93.3	91.3	95.8	91.7
60–69	75.0	98.4	97.3	94.4	94.2	96.0	91.7	70.4
Total	73.0	97.5	95.0	95.4	95.1	95.7	96.6	85.4

Table 6 Correlation between degree of *H. pylori* infection and other pathological findings in each biopsy site

Pathological finding	Degree of pathological finding								Correlation coefficient[b]
	None		Light		Moderate		Severe		
	Mean[a] HP score	No. of biopsies	Mean HP score	No. of biopsies	Mean HP score	No. of biopsies	Mean HP score	No. of biopsies	
Infiltration of polynuclear cells									
Epithelium	1.12	(2782)	1.77	(3332)	1.97	(1077)	2.15	(33)	0.400
Stroma	0.78	(1289)	1.55	(3186)	1.88	(2474)	2.21	(269)	0.463
Lumen	1.52	(6654)	2.02	(522)	1.68	(22)	1.00	(3)	0.144
Infiltration of monocytes	0.29	(224)	1.27	(2780)	1.79	(3828)	2.02	(384)	0.408
Active regeneration	1.14	(2461)	1.73	(3664)	1.91	(1045)	2.00	(24)	0.352
Atrophy	1.61	(4564)	1.60	(1088)	1.35	(404)	0.60	(102)	−0.131
IM	1.61	(6169)	1.48	(457)	1.27	(391)	0.62	(204)	−0.201
Dysplasia	1.56	(7090)	1.06	(108)	0.67	(18)	1.50	(4)	−0.083

[a] Degree of *H. pylori* infection (HP score) was graded as 0, none; 1, difficult to find; 2, easy to find; and 3, abundant.
[b] For all correlation coefficients $P < 0.01$.

Table 7 Review of the prevalence of precancerous lesions in various countries and comparison with Venezuela

Country	Reported by	Age (yr)	No. of biopsies	Prevalence (%)			ASIR of gastric cancer[a]
				AG	IM	DYS	
Japan	Yamakawa *et al.* (12)	30–69	8		75		74.8
China	You (13)	35–64	7	98	53	20	49.8
Colombia	Correa (3, 4)	35+	4+	57	38	10	36.3
Estonia	Villako (14)	16–69	4	41			37.0
Hungary	Cheli (15)	20–79	2	37	24		26.9
Italy	Cheli (15)	20–79	2	22	11		26.8
Finland	Ihamäki (16)	46[b]	3+	27	18		20.7
UK	Sitas (17)	20–69	5	55	17		17.8
France	Potet (18)	53[b]	5	38			14.5
Venezuela	This study	35–69	5	49	34	6.5	49.6

[a] ASIR, Age-standardized incidence rate/100,000 for males [from Parkin *et al.* (19–20).
[b] Mean age.

the Colombian survey in which a design similar to the one used in the present study was used (3). The two populations are also similar from the point of view of stomach cancer risk, dietary habits, and other factors. Compared with the prevalences in these Latin American countries, those in Japan (12) and in China (13) are higher and those in European countries are lower (15–18), a pattern similar to that of gastric cancer risk (19, 20).

In this study, a marked decreasing trend in the prevalence, both overall (based on all biopsies) and on the global diagnosis (based on the most severe lesion), with advancing stage of precancerous lesions has been observed. This finding is consistent with the hypothesis that these lesions of the gastric wall are sequential in the natural history of gastric cancer (3) and should, therefore, be regarded as precancerous lesions. Their sequential evolution is also suggested by the age distribution of the lesions; when the global diagnosis is considered, less advanced lesions decrease in prevalence, whereas the more severe ones increase with age.

Less advanced lesions, especially CG, tend to be diffuse or multifocal, as shown by the high number of biopsies and subjects in which this diagnosis is made. In contrast, more severe lesions, such as IM and dysplasia, tend to be unifocal, emphasizing the need of efficient sampling of the gastric mucosa for such diagnoses.

It has been shown that subtyping IM by mucin histochemistry is useful in predicting the risk of stomach cancer. Type III

(sulfomucin-positive/incomplete IM) indicates the highest risk for subsequent stomach cancer, and type II (nonsulfated/incomplete IM) indicates an intermediate risk (21). The proportion of type III metaplasias over all metaplasia cases in our study population (24%) was close to that seen in Slovenia (27%), where the risk of stomach cancer is also high (21).

The analysis of pathological lesions by type of gastric mucosa (fundic or antral) shows that the antral mucosa is far more affected by all types of lesions. However, it should be noted that in this study the fundic mucosa is less represented among the biopsies than is the antral one because a majority of subjects have only one fundic biopsy, whereas they have four or five antral biopsies.

The prevalence of *H. pylori* infection in our population was among the highest reported on the basis of histological diagnosis. A prevalence of 70–95% in adults ages 20–60 years was reported in Peru (22), and a level of 73% was reported in Ethiopia (23). Among developed countries, its prevalence was 50% in Finland (24) and 32% in the United States (25). *H. pylori* infection has been associated with risk of gastric cancer (6–7); its high prevalence in Venezuela is consistent with this hypothesis. In developing countries, the prevalence of *H. pylori* infection and of gastritis begins to rise early in childhood (5). The lack of subjects below 35 years of age in our study group precludes verifying if this is the case also in Venezuela because at the age of 35 years almost all subjects were already infected with *H. pylori* and showed some kind of gastric lesion. In this study, the prevalence of *H. pylori* was extremely high (95%) in subjects with AG and IM, whereas subjects with SG and dysplasia are slightly less frequently affected. This result is not consistent with other studies in which IM and AG have been shown to be less favorable environments for *H. pylori* development (5). On the other hand, when the score of *H. pylori* infection is correlated with the type of concomitant gastric lesion, a high positive correlation coefficient is shown for all signs indicative of CG, whereas a negative correlation is identified with increasing grade of atrophy, IM, and dysplasia, suggesting that when the pathological lesions of the gastric wall are more severe, the gastric environment becomes slightly less suitable for *H. pylori* colonization. The causal association between *H. pylori* and CG is supported by our data because the degree of infiltration of mono- and polynuclear cells and of active regeneration, both indicators of the severity of the gastritis, is very positively associated with the burden of *H. pylori* infection. Similar associations have been described in the population of Finland (26).

In conclusion, this cross-sectional study on the prevalence of gastric lesions and *H. pylori* infection in Venezuela shows a high prevalence of SG, CG, IM, and dysplasia and of *H. pylori* infection in a population at high risk for gastric cancer and supports the precancerous nature of these gastric lesions.

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