First-degree relatives of patients with gastric cancer have high frequencies of achlorhydria and premalignant gastric lesions

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Abstract

Objective: The objective of this study was to establish the frequency of preconditions for gastric cancer including atrophy, metaplasia, dysplasia and achlorhydria (pH > 5) in first degree relatives of patients with gastric cancer (FDR-GC). **Design**: This is a prospective case-control study with incidental cases. **Patients:** One hundred twelve first degree relatives of gastric cancer patients (case group) were paired by age and gender to 117 patients with functional dyspepsia but without GC family history (control group). **Study location:** This study was conducted in the gastroenterology service of a level three hospital in Bogotá, from March 1st, 2011 to March 31st, 2012. **Procedures conducted:** High digestive endoscopy, gastric pH measurements and gastric biopsies were performed. **Measurements:** We evaluated and compared endoscopic and pathological measurements as well as measurement of gastric pH. **Results:** The case group's 60 % frequency of pangastritis was higher than the control group's 28.8% (OR 3.32, CI 1.92 to 5.74, p < 0.05). There were findings suggestive of atrophy in 19.6% of the case group patients and in 7.7 % of the control group (OR 2.65, CI 1.16 to 6. 04, p < 0.05), findings suggestive of intestinal metaplasia in 12.5% of the case group and 0% of the control group, alkaline pH in 35.7 % of the case group and 7 % of the control group (OR 5.94, CI 2.72 to 12.98, p < 0.05). There were 4 cases of low grade dysplasia, two cases of high grade dysplasia (P <0.005), and two of early GC (NS). **Conclusions:** FDR-GCs had more achlorhydria, premalignant conditions, dysplasia and GC than control patients. The measurement of gastric pH is sensitive for detecting gastric atrophy. FDR-GC patients should be routinely screened with endoscopy and gastric pH measurement.

Key words

Gastric cancer, relatives, atrophy, metaplasia.

INTRODUCTION

Gastric cancer (GC) is a pathology that has a great impact on global morbidity and mortality, especially in countries such as Japan and Colombia. It is one of the most frequently occurring malignant tumors and is the first cause of death by cancer (1-3). In our country it occupies second place within the neoplastic pathologies and causes 15% of the deaths by cancer (2). Although incidence, diagnosis and therapeutic options have changed greatly in recent decades, GC's prognosis continues to be poor: GC patients have a survival rate below 10% because more than 90% of them are diagnosed when the cancer is in advanced stages (1). In 2012, in the United States alone, there were approximately 21,320 new cases diagnosed. Of these, 10,540 (49%) are expected to die (4). Histologically, there are two types of GC: intestinal and diffuse. The first is more common, and more risk factors have been identified for it. *Helicobacter pylori (H. pylori)* infections are the etiological agent in at least 90% of cases (5). Diffuse type is less frequent, is observed in young people, and has a worse prognosis (6). The physiopathology of intestinal type cancer has yet been not sufficiently well explained, but it is considered that it does not occur spontaneously but rather occurs as a result

of chronic inflammatory changes triggered by *H. pylori* over 15 to 20 years (7). This carcinogenetic pathway has been hypothesized for intestinal cancer. In 1975 Dr. Pelayo Correa proposed the existence of a sequential progression from chronic gastritis through atrophic gastritis, intestinal metaplasia, dysplasia, early adenocarcinoma and finally to advanced cancer (8). Nevertheless, GC is multifactorial, and it is considered that there are also genetic factors required for its development. These factors interact with environmental factors such as smoking, high salt intake and – most importantly - *H. pylori* infection to lead to the appearance of this tumor. *H. pylori* infection is a necessary, but not a sufficient factor (5, 9). In 1994 the International Agency for Research on Cancer (IARC) named *H. pylori* a Type I carcinogenic agent (10). At present it is considered to have a variable effect on carcinogenesis which depends on virulence factors such as cagA and vacA genes (11-14). The genetic component is illustrated by the fact that GC is more frequent in individuals with histories of gastric cancer in first degree relatives (9, 11, 15, 16). According to the literature, between 5% and 10% of gastric cancer patients have family histories of the tumor (17-19). while other authors have established that the risk for those with family histories of GC is two to three times more than that of the general population (19). Nevertheless, family history is much more important for diffuse cancer than for intestinal type GC, especially when the first-degree relative with diffuse cancer was under 40 years of age. In addition, some families have hereditary diffuse GC syndrome (20). Multiple studies have evaluated the relationship of family histories of GC and *H. Pylori* infections, and one recent study showed an odds ratio of 1.94 (21). Two recently published Colombian studies have shown that one of the main risk factors for patients with family histories of GC is when first-degree relatives have this illness (22, 23). On the other hand, one of the main components in Dr. Correa's carcinogenesis cascade is gastric atrophy which is associated with parietal cells loss due to secondary reduction of acid production. Hypochlorhydria and compensatory increases of serum gastrin act to induce proliferation of gastric epithelial cells and also favor colonization of bacteria that are capable of transforming nitrates from dietary to mutagenic agents such as N-nitrous compounds (5, 15). Consequently, detection through panendoscopy (PES) becomes important even though it has poor sensitivity and specificity and biopsies are required to determine the presence of atrophy. Requiring biopsies from all of these patients creates additional expenses and requires the involvement of the pathologist and therefore cannot be very cost effective (15). As previously mentioned, one of the consequences of atrophy is the reduction or elimination of acid (achlorhydria), however detection of atrophy by examining gastric acid is very bothersome and expensive and is not widely used. In a recently published study litmus paper was used to measure the pH of the gastric acid (16). This method effectively identified achlorhydria as an atrophy indicator with excellent correlation to histology. This is a very economic and easy to use method which has been proposed for routine use in our environment to establish the gastric pH of the patients who undergo endoscopy. This method was previously described by Levine and colleagues in 1994 when this author utilized it to measure the pH of vacuumed gastric samples from UCI patients. That study compared the method with pH measurement with an electrode placed on a probe to measure the pH. The excellent correlation between the two methods was excellent (R^2 = 0.93, $p < 0.001$) (24).

Keeping in mind the family component of GC and the possibility of determining the presence of atrophy by measuring gastric pH as an indicator of achlorhydria or hypochlorhydria (pH >5), we decided to undertake this study to estimate the frequency of atrophy and metaplasia which are precursors of GC, premalignant lesions (dysplasia), and hypochlorhydria (pH>5) in first degree relatives of people with gastric cancer (FDRGC). If it can be proven that FDRGC have higher risks of GC (as shown in the literature), and if GC develops over decades from a cascade of inflammatory events, it should be possible to evaluate FDRGC with endoscopy, biopsies and pH measurement and to diagnose lesions opportunely prior to the onset of GC during the early stages of GC when has greater than 90% probability of achieving a cure (25-28). This could prevent us from continuing to face advanced GC with its awful prognosis with a 5 year survival rate of less than 10% (4).

MATERIALS AND METHODS

This is a prospective case and control study undertaken in the gastroenterology service of Hospital El Tunal and the gastroenterology unit at the Universidad Nacional de Colombia. This study was conducted between March 1, 2011 and March 31, 2012. All non-cardiac GC cases confirmed by pathology (37 patients) were identified, and their first-degree relatives were invited to participate. There were 185 potential participants, but only 112 people accepted the invitation to be included in the study. These people became Group I and were labeled first degree relatives of people with gastric cancer (FDRGC). In the structure of this study, the FDRGC group corresponds to cases. They were paired by age and gender with 117 patients who had been diagnosed with functional dyspepsia during the same period of study in our service but who did not have family histories of GC. These patients constitute the control group which was labelled Group II.

All patients signed informed consent forms in order to participate in this study which work was approved by the research committee of the institution in which it was carried out. A gastroenterologist filled out a data collection form for every participant. The document recorded the patient's identification, history, and time of onset of symptoms. Subsequently all patients from both groups underwent panendoscopy without sedation but with topical anesthesia following a minimum 8 hour fast. An Olympus Exera II endoscope was used. All procedures were carried out by the same gastroenterologist (MG) to avoid interobserver bias. As part of the bias control strategy, the endoscopist did not know the data recorded on patient questionnaires. Once the endoscope was in the patient's stomach, the gastric mucous lake was vacuumed into a container. A strip of litmus paper was then dipped into the material collected to measure its pH. Hypochlorhydria was diagnosed when the litmus paper strip showed a pH above 5 according to the method described in the literature (16). The Sydney protocol was followed for staging chronic gastritis. It recommends taking two biopsies from the corpus 8 cm from the cardia, one from the anterior wall and one other from the posterior wall; and two more biopsies from the antrum 2 or 3 cm from the pylorus, one from the greater curve and one from the lesser curve; and one biopsy from the angular incisure (29). An additional biopsy was taken for the rapid urease test for *H. pylori* infection.

Inclusion Criteria

- Group I (cases): Patients older than 18 years, histories of with gastric cancer in first-degree relatives.
- Group II (controls): Patients older than 18 years, with functional dyspepsia, without histories of with gastric cancer in first-degree relatives.

Exclusion criteria for both groups

Presence of a gastric bile lake that could give false negative results for hypochlorhydria because of alkalinity of the gastric acid, use of PPIs in the two weeks prior to examination, previous treatments for *H. pylori* eradication.

STATISTICAL ANALYSIS

Information was entered into Excel 2007 and analyzed with Stata 10.0. Descriptive statistics were used to describe variables in the study. Frequency distributions and percentages were used to analyze nominal and ordinal variables. Numerical variables were expressed with central tendencies and dispersions. Statistical tests were evaluated to a degree of significance of 5% ($p<0.05$). Continuous variables were informed as frequencies and averages. The differences between averages were determined with the Student's t test.

RESULTS

In our work two groups of patients were compared: a group without family histories of gastric cancer and one with family histories of gastric cancer. The number of patients in each group was similar (117 and 112 respectively) as were age ranges, gender distributions, and distributions of smoking habits and alcohol intake (Table 1).

Table 1. General characteristics.

Variables	Group I Family history n=112	Group II No family history n= 117	OR	95 % CI	P
Age	39 (21-57)	38 (18 -59)			
Male	38.6%	35.6%	0.96	0.56 - 1.65	0.9
Smoking	19.5%	17.9%	1	0.51 - 1.94	0.99
Alcohol	18.50%	20.2%	0.8	0.41 - 1.54	0.5
Dyspepsia	75%	100%			
Asymptomatic	25%	No			
Symptomatic	6 m (2-24)	5 m (3 -12)			

A comparison of endoscopic findings from the two groups (Table 2) showed that the FDRGC group had a greater frequency of pangastritis (60%) than the control group (28.8%) OR 3.32 (CI 1.92 -5.74 $p< 0.05$), more frequent findings suggestive of atrophy such as increased vascular indications and thin mucosa (19.6) than the control group (7.7%) OR 2.65 (CI 1.16 – 6. 04 $p < 0.05$), more indications of intestinal metaplasia such as dental plaque (12.5%) than the control group (0%), and had alkaline pH (35.7 %) more often than the control group (7%), OR 5.94 (CI 2.72 – 12.98 $p < 0.05$) (Figures 1 and 2).

Histologic findings (Table 3) showed a higher frequency of atrophy among FDRGC patients (39.3 %) than in control patients (10.3%) OR 5.02 (CI 2.47 – 10, 17 $p < 0.05$). Six cases of dysplasia cases were found in the FDRGC group: four were low grade and two were high grade but without any apparent focal lesion. In addition, in this group two cases of early GC were found. They were treated endoscopically. No cases of advanced GC were found (Figure 3).

DISCUSSION

This study found that the FDRGC group had greater risks of pangastritis than did the control group (OR 3.32, CI 95% 1.92–5.74). Antral gastritis, which is not related to

Table 2. Endoscopic findings FDRGC vs. dyspepsia.

Variables	Group I Family history n=112	Group II No family history n= 117	OR	95 % CI	P
ph> 5 (atrophy)	51.8	20.6	3.6	2.02 - 6.43	< 0.05
pH < 5	48.2	79.4	0.17	0.09 - 0.32	< 0.05
Normal lake	96.4	94	0.21	0.04 - 1.03	0.0367
Panendoscopy					
Antral gastritis	20.6	56.4	0.17	0.09 - 0.30	< 0.05
Corporal-antral	8.9	15.4	0.48	0.21 - 1.10	0.0823
Pangastritis	60.7	28.2	3.32	1.92 - 5.74	< 0.05
Metaplasia	12.5	0			
Atrophy	19.6	7.7	2.65	1.16 - 6.04	0.0173
Gastric ulcer	0	2.6			
Duodenal ulcer	1.8	5.1	0.3	0.06 - 1.55	0.1329

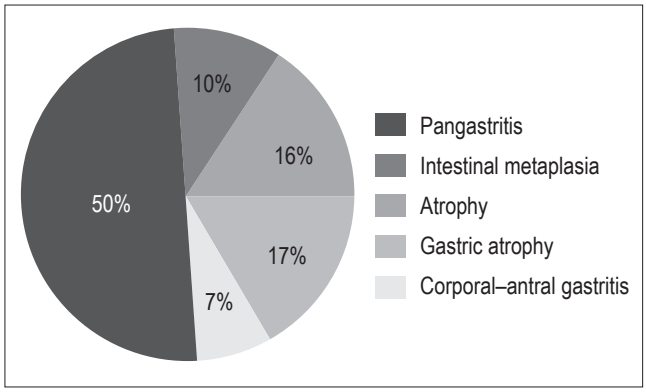

Figure 1. Endoscopic findings from FDRGC Group.

Table 3. Histological findings from FDRGC group vs. control group.

Variables	Group I Family History n=112	Group II No Family History n= 117	OR	95 % CI	P
Intestinal metaplasia	27.7%	7.5%			0.005
Corpus atrophy	14.3	2.6	5.75	1.62 - 20.34	0.0026
Antrum and corpus atrophy	19.6	7.7	2.65	1.16 - 6.04	0.0173
Without atrophy	60.7	89.7	0.09	0.03 - 0.21	< 0.05
Any degree of atrophy	39.3	10.3	5.02	2.47 - 10.17	< 0.05
HP	76.2	84.6	0.34	0.17 - 0.70	0.027
pH and atrophy correlation	82.1	89.7	0.3	0.13 - 0.68	0.029
Dysplasia	5.3%	0			< 0.05
Low degree	4 cases	0			
High degree	2casos	0			
Early gastric carcinoma	2 (1.78%)	0			NS

GC, was predominant among control group patients (5). Pangastritis is the type of gastritis present in patients with GC (5,30). Atrophy occurred almost four times more often in group I than in the control group (OR 5.02 (CI95%2.47-10.17). Atrophic gastritis with or without metaplasia is considered to be the main precursor lesion to GC and the field upon which cancer forms (31). The correlation between endoscopic suspicion of atrophy and histological confirmation was 19.6% which proves once again that diag-

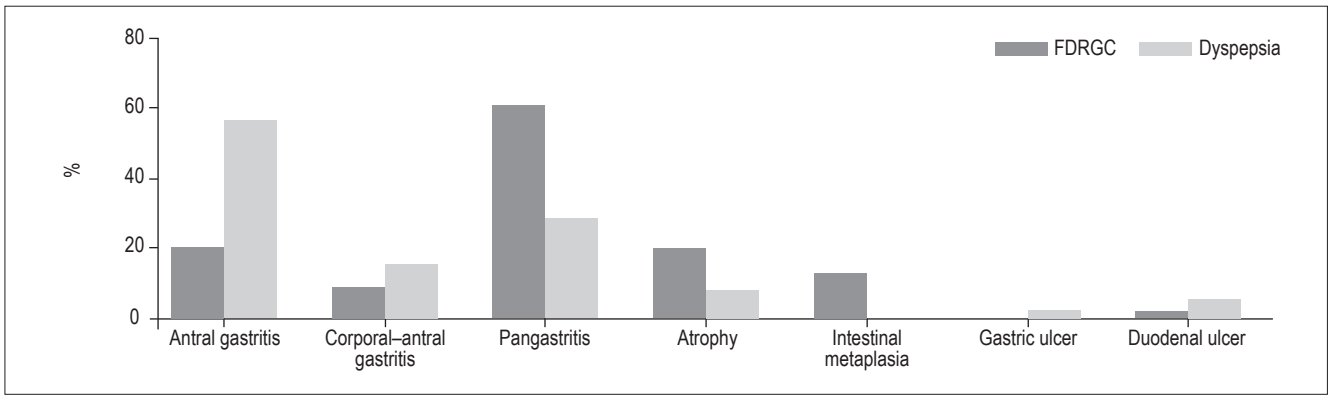

Figure 2. Endoscopic findings from FDRGC Group vs. Control Group dyspepsia.

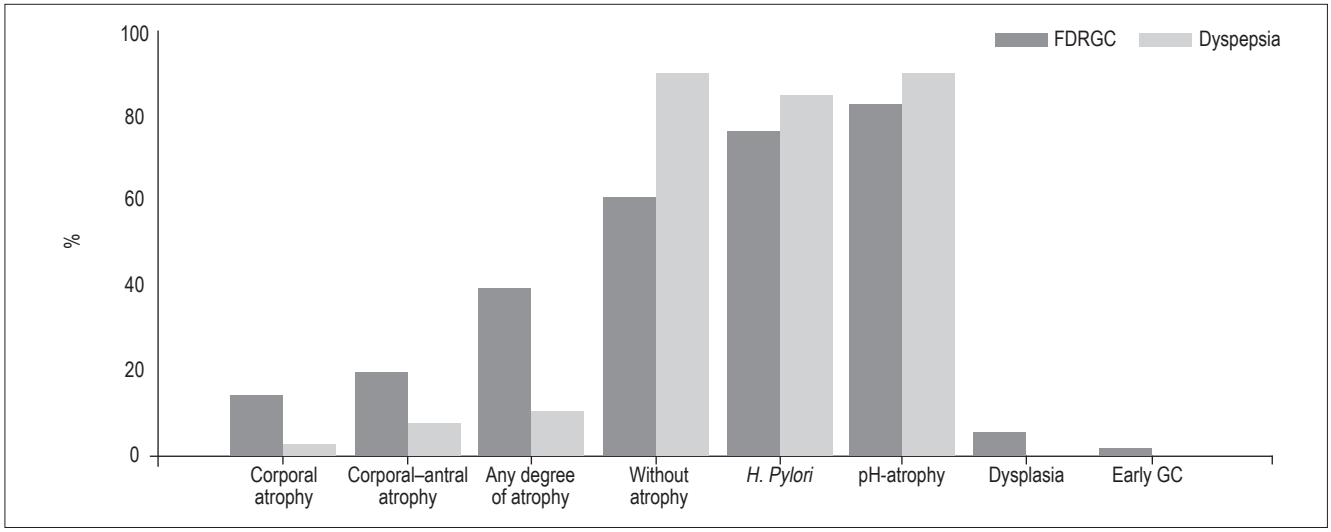

Figure 3. Histological findings from FDRGC Group vs Control Group.

nosis requires histological study as expert researchers have already said (17). Histology is also the only means for staging GC risk in accordance with the severity of atrophy, so it is a necessity for planning strategy for monitoring these patients (32). After evaluating the pH with litmus paper, we found that the probability of reversing hypochlorhydria was greater in Group I than in the Group II (OR 3.6, 95 % CI 2.02 – 6.43) and that this measurement had a strong linear correlation with histologic findings of atrophy with an r^2 of 0.82. In contrast, most control group patients had pH below 5 indicating that acidity correlates with low frequencies of atrophy (10%). Over 10 years ago a study by El-Omar and colleagues with a design to that of this study evaluated gastric pH with a more complex and more expensive method (33). People with family histories of GC history were compared to patients with dyspepsia without family histories of GC. They found that the frequency of hypochlorhydria was 27% in the group with family histories of GC, but only 3% in the group without such histories. Similarly they found a rate of atrophy of 34% in the FDRGC group, but only 5% in the control group. Not surprisingly given the high frequency of *H. pylori* infections in our population, both groups had high incidences of *H. pylori* infections: 82.1% for FDRGC and 89.7% for the control group (22). The fact that the frequency of this microorganism was similar in the two groups reinforces the idea that this infection alone is not sufficient to cause GC. Its appearance requires additional factors such as the environment, the diet, and genetics (family history). Among the conditions that are precursors for GC, intestinal metaplasia (IM) was found in 27.7% of the biopsies from the FDRGC group but only in 7.5% of the control group ($p<0.05$). The high frequency of IM in Group I further corroborates that Group I patients have higher GC risks than do Group II patients since IM is more advanced than atrophy in the chain of carcinogenic events (8, 9, 15). Another advantage of histology is that its diagnostic has less inter-observer variability (34, 35). Poor correlation (12.5%) between endoscopic suspicion of IM and histological diagnosis of IM confirms that endoscopy alone is not reliable for a definite diagnosis of these premalignant conditions. In addition to the greater frequency of atrophy and metaplasia in Group I, dysplasia was found in six of these patients (four low grade cases and two high grade cases). Since the two high grade cases were similar to early GC in situ, these lesions were endoscopically removed in accordance with the current recommendation for such alterations (28). Patients with low degree dysplasia are currently being monitored endoscopically every six months. None of these types of lesions were found in the control group. Taking these findings in the patients of the FDRGC group together and comparing them with the findings from the group of patients with dyspepsia without GC family histories of GC shows that an accelerated process of carcinogenesis exists among FDRGC group patients. In addition to *H. pylori* infections, risk factors may include genetic susceptibility and environments favorable to GC which are similar to the environments of relatives and which include factors such as diet, habits of life and overcrowding. The results of this study corroborate findings of a previous study which showed that patients with GC family histories had higher risks for developing this tumor than did patients with duodenal ulcers (22).

Atrophy, intestinal metaplasia, dysplasia and early GC findings from Group I patients, support Doctor Correa's gastric carcinogenesis hypothesis (8). In addition, they imply that conducting endoscopies in FDRGC patients should have a high probability of timely detection of

lesions and premalignant conditions. Moreover, it implies that these patients should continue in an endoscopic surveillance program in which early detection of GC would result in timely treatment through endoscopic resection. This would allow it to heal itself as has been shown by diverse researchers (23, 28). Finally, it would end the tragedy in which cancer is usually detected in our country in advanced stages in which surgery or palliative treatments - with their high human and financial costs - are the only alternatives that can be offered to patients.

With the results of this study, we want to highlight that measuring gastric acid with litmus paper is easy to execute and correlates extremely well with histological findings. It requires only a minute to determine whether the vacuumed sample's pH is alkaline indicating atrophy, or acid indicating absence of atrophy. This corroborates recently published findings (9). As far as we know, this is the first study that measures pH through endoscopy and which correlates these results with the results of histology for people with family histories of gastric cancer. With this methodology we have shown that atrophy and hypochlorhydria occur more frequently among this group of people than they occur among patients with functional dyspepsia but no family histories of GC. Atrophy and hypochlorhydria are two conditions that have been clearly identified by diverse authors as risk factors for GC which explains so many more cancer cases are found in this population. (7, 8, 36, 37, 38). The higher than 80% correlation above between histology and pH measurements that this study found allows us to recommend this innovative method as a histologic alternative for establishing or dismissing gastric atrophy. It has the additional advantages of being simple and very economical when compared to other methods used to measure gastric acidity with probes, complex devices and expensive medicine such as pentagastrin (39).

One weakness of our work was that we did not use the OLGA staging system to rank results from pathology reports and to correlate them with our endoscopic findings. Some studies (40) have shown that patients classified as OLGA III/IV have a higher risk of atrophy and therefore of cancer (41). Nevertheless, this classification requires five biopsies and a pathologist to evaluate them. For these reasons our group decided to classify atrophy into only two categories: absent or present. In addition, evaluation of atrophy has great inter-observer variability and does not take into account. Even though atrophy has an inherent GC risk, recent reports have shown that metaplasia is a premalignant condition which is much more relevant in the process of gastric carcinogenesis (42, 43). For this reason, it has recently been proposed to stage intestinal metaplasia using the OLGIM scale (44).

CONCLUSIONS

1. Patients with dysplasia who have first-degree relatives of patients with gastric cancer more frequently develop hypochlorhydria, dysplasia, and gastric cancer and have more premalignant conditions than do control patients with dysplasia.
2. The litmus paper method of measuring acidity of a vacuumed gastric sample is innovative, simple, very economic and highly sensitive for detecting gastric atrophy (hypochlorhydria).
3. Patients with family histories of GC must be screened with endoscopy including measurement of the gastric pH because of the high risks they run of developing GC precursor conditions such as atrophy, intestinal metaplasia, dysplasia, and early GC which are susceptible to endoscopic treatment.
4. It would be interesting to continue this research about pH measurement with litmus paper by correlating it with the recently described OLGA system that stages GC risks in accordance with atrophy.

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