

Prevalence and Associated Factors of Premalignant Lesions in Patients with *Helicobacter Pylori* Infection

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ABSTRACT

AIM: *Helicobacter pylori* has revolutionized our thinking on gastric carcinogenesis. However, given the low percentage of infected patients who develop gastric cancer, one may hypothesized the presence of factors involving in the carcinogenesis. The aim of our study was to evaluate the prevalence of premalignant lesions: gastric atrophy and intestinal metaplasia in a population infected with *Helicobacter pylori*; and to investigate about the factors predicting their development.

METHODS: This is a prospective study, including 481 patients with *H. pylori* infection confirmed by histological study of gastric biopsies performed per endoscopy.

RESULTS: Among our patients we had 216 (44.9%) women and 265 (55.1%) men. Chronic antral gastritis was found in 478 of patients (99.4%) and chronic fundic gastritis in 405 of patients (84.4%). The prevalence of gastric dysplasia was 0.4%. In our patients 12,6% had gastric atrophy and 7.7% had intestinal metaplasia. Multivariate analysis showed that only the activity of gastritis is an independent risk factor for the premalignant lesions: Gastric Atrophy: Antrum (OR = 2.66; $p < 0.001$), Fundus: (OR = 2.09; $p = 0.01$). Intestinal metaplasia: Antrum: (OR = 1.82; $p = 0.011$) Fundus (OR = 1.8; $p = 0.02$).

CONCLUSION: The prevalence of gastric atrophy and intestinal metaplasia in patients infected with *Helicobacter pylori* remains low compared with other countries. The activity of gastritis is significantly associated with these premalignant lesions.

Key words: *Helicobacter pylori*; Gastritic Atrophy; Intestinal metaplasia

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INTRODUCTION

The *Helicobacter pylori* infection (*H. pylori*) is as major risk of gastric carcinoma. Thirty years ago Correa hypothesized the cascade of histological steps involved in the process of carcinogenesis: so there is changes of the gastric mucosa from non-atrophic gastritis to atrophic gastritis, intestinal metaplasia, dysplasia and finally invasive cancer^[1]. In 1998, Watanabe *et al*^[2] established that Mongolian gerbils with persistent infection with *H. pylori* developed gastric adenocarcinoma. A long-term, prospective study in Japan showed that gastric adenocarcinoma develops in patients infected by the bacteria and does not develop in those who are not infected^[3]. On the basis of these clinical and epidemiological observations, we can deduce the involvement of *H. pylori* in the process of carcinogenesis; as a

result, the bacterium has been classified by the International Agency for Research on Cancer of the World Health Organization as a class I carcinogen in 1994^[4]. However, the prevalence of infection is high in asymptomatic population and only a few subjects develop cancer. In this context, some African epidemiological studies revealed that there is no correlation between *H. pylori* and the risk for gastric cancer^[5]. Furthermore, the *H. pylori* infection is widely diffused in Asian countries but the prevalence of gastric cancer in these countries is low^[6]. The African and Asian enigma suggests that additional factors may be advocated to explain the outcomes of *H. pylori* infection and the processes of gastric carcinogenesis. To our knowledge, no study has assessed the prevalence of *H. pylori* in Moroccan population. We therefore carried out this prospective study to investigate the predictive factors of premalignant lesions in a population infected with *H. Pylori*.

MATERIALS AND METHODS

Patients

This is a prospective, open, monocentric, descriptive and analytical study conducted between January 2010 and March 2015 in the department of Gastroenterology and Digestive Endoscopy, Mohamed V Military Teaching Hospital, including 481 adult patients of both sex in whom the infection with *H. pylori* has been identified by histological examination. Exclusion criteria were previous treatment against *H. pylori*, and patients with pathology other than *H. pylori* that may explain gastric atrophy eg: Biermer anemia.

Endoscopy

All patients received gastric biopsies performed per endoscopy; classified according to the modified Sydney System: two biopsies at the antrum, a biopsy at the angulus and two at the fundus.

Histology

Biopsy specimens were analyzed histologically for *H. pylori* (Hematoxylin Eosin stain) and for bacterial density (Giemsa stain).

Bacterial density, degree of inflammatory activity (presence of a polymorphic inflammatory infiltrate in the lamina propria, epithelium and crypts) and atrophy were graded on a semi-quantitative scale (0: absent; 1: low; 2: moderate; 3: severe). Intestinal metaplasia and dysplasia have also been noted.

Statistical Analysis

For each of our patients, we filled in pre-established operating records, including socioeconomic, endoscopic and pathological data. We performed the statistical analysis with Statistical Package for the Social Sciences (SPSS ®) version 10.1, Chicago, IL. The categorical variables are expressed in number and percentage. The quantitative variables are expressed as mean and standard deviation for Gaussian distributions variables, and median and interquartile ranges for non-Gaussian distribution variables. Kolmogorov -Smirnov test, evaluated normality. The study of predictive factors of premalignant lesion was performed using binary logistic regression in univariate and multivariate models. The risk of error was set at 5%, A *p* value < 0.05 was considered to be significant.

RESULTS

Clinical data

We included 418 patients infected with *H. pylori*. Among our patients we had 216 (44.9%) women and 265 (55.1%) men. The

mean age was 43.67 ± 13.42 with extremes ranging from 16 to 84 years. Chronic smoking was found in 89 of patients (18.5%), and 5(1%) of patients had a family history of gastric cancer. Clinical symptomatology is dominated by atypical epigastralgia, found in 181 patients (37%) (Table 1).

Histological results

Chronic antral gastritis was found in 478 of patients (99.4%) and chronic fundic gastritis in 405 of patients (84.4%). The frequencies of severe gastritis were 3.1% in Fundus and 11.9% in Antrum (Figure 1). The density of *H. pylori* was high in 6.7% of patients in Fundus and in 23.6% of patients in Antrum (Figure 2). With regard to gastric dysplasia it was found in only 0.4% of patients. Among our patients, 12.6% had gastric atrophy and, 7.7% patient had intestinal metaplasia (Figure 3).

Predictive factors of premalignant lesion

Univariate analysis of the clinical and histological data demonstrated that the age and the activity of gastritis were significantly associated with the premalignant lesions (Gastric atrophy and intestinal metaplasia). Multivariate analysis with logistic regression showed that only the activity of gastritis is an independent risk factor for the premalignant lesions: Gastric Atrophy: Antrum (*p* < 0.001; OR = 2.66; 95% IC: 1.80-3.9), Fundus: (*p* = 0.01; OR = 2.09; 95% IC: 1.37-3.19). Intestinal metaplasia: Antrum: (*p* = 0.011; OR=1.82; 95% IC: 1.14-2.90) Fundus (*p* = 0.02; OR = 1.8; 95% IC: 1.01-2.95) (Tables 2 and 3).

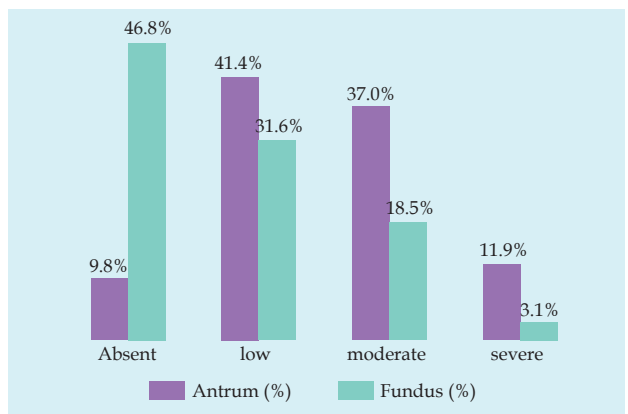


Figure 1 The activity of gastritis in the antrum and the fundus.

Table 1 Demographic and clinical Data.

Age mean ± (years)	43.67 ± 13.42
	n (%)
Gender	
Male	216 (44.9)
Female	265 (55.1)
Family history of gastric cancer	5 (1)
Chronic smoking	89 (18.5)
Ulcerative syndrome	94 (19.5)
Dyspepsia	42.6 (23.1)
Epigastralgia	181 (37.6)
Gastroesophageal reflux	48 (10)
Vomiting	8 (1.7)
Gastrointestinal bleeding	21 (4.4)
Anemia	12 (2.5)

DISCUSSION

Two histologically variants of Gastric adenocarcinoma have been described: The diffuse-type is associated with sporadic or hereditary mutations of the *cdh1* gene encoding E-cadherin, which inhibit the overpressure of this molecule at the level of adherent cell junctions. Whereas the development of intestinal gastric adenocarcinoma is a multistep process of histologically well-characterized events ranging from chronic gastritis to atrophy, intestinal metaplasia, dysplasia, and finally adenocarcinoma^[7].

Correa and Houghton have shown that the infection of *H. pylori* is the triggering event of this cascade^[11]. Nonetheless according to their finding adenocarcinoma occurs in less than 1% of *H. pylori* infected subjects; it is suggests that other factors are involved in the carcinogenic process, and could further explain the variation of prevalence of gastric carcinoma in *H.pylori*-infected individuals among different geographical areas.

Our study showed that gastric atrophy developed in 12.6% and intestinal metaplasia in 7.7% of *H. pylori* infected patients. It is noteworthy that the prevalence of premalignant lesion in the present study is lower than other investigations. Kupiers *et al* found that atrophic gastritis developed in 29% infected patients, in agreement with another Japanese study, in which the prevalence of atrophy was 22%^[8]. In regards to intestinal metaplasia, Harry Hua-Xiang finds that it was present in 22.1% of H-pylori positive patients^[9]. In Tunisia the prevalence of gastric atrophy and intestinal metaplasia were respectively 35% and 11% in patients with *H. pylori* infection^[10]. Our opinion is that methodological aspects could

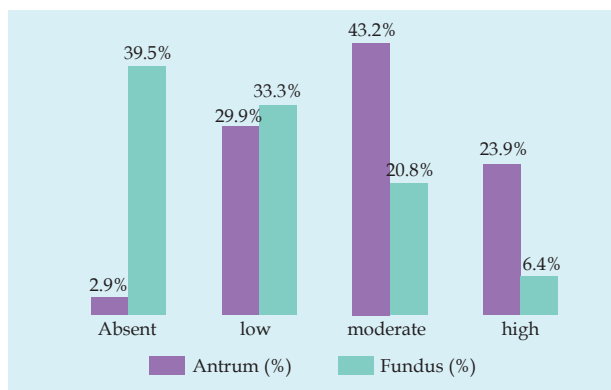


Figure 2 The density of *H.Pylori* in the antrum and the fundus.

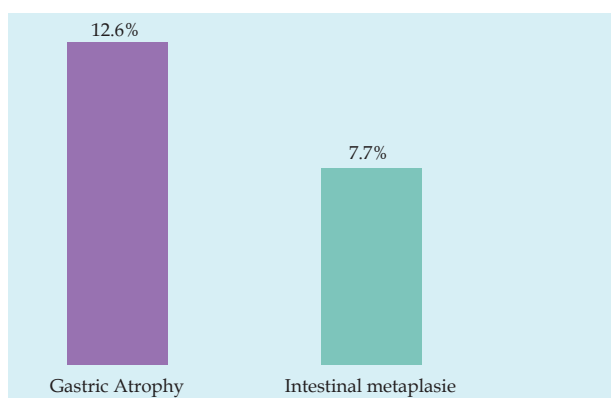


Figure 3 Prevalence of premalignant lesions.

Table 2 Univariate and multivariate analyses for factors related to gastric atrophy.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% IC	P-Value	OR	95% IC	P-Value
Age	1.01	[0.1-1.04]	0.08	1.02	[1.00-1.04]	0.04
Gender	0.9	[0.5-1.5]	0.6			
Chronic smoking	1.4	[0.70-2.70]	0.3			
Family history of gastric cancer	0		0.9			
Antrum						
Gastric Activity	2.9	[2.00-4.20]	<0.001	2.66	[1.80-3.90]	<0.001
Density of H.Pylori	1.35	[0.96-1.92]	0.08			
Fundus						
Gastric Activity	1.1	[1.45-2.65]	<0.001	2.09	[1.37-3.19]	0.001
Density of H.Pylori	1.2	[0.90-1.60]	0.2	1.66	[0.43-0.99]	0.04

OR: odds ratio, IC: confidence interval, GC: History family of gastric cancer.

Table 3 Univariate and multivariate analyses for factors related to intestinal metaplasia

Variables	Univariate analysis			Multivariate analysis		
	OR	95% IC	P-Value	OR	95% IC	P-Value
Age	1.03	1.00-1.05	0.024	1.03	[1.00-1.06]	0.014
Gender	0.93	0.47-1.83	0.6			
Chronic smoking	0.63	0.25-1.77	0.419			
GC	3.05	0.33-28.06	0.324			
Antrum						
Activity	2.13	1.39-3.27	0.001	1.82	[1.14-2.90]	0.011
Density of H.Pylori	1.17	0.77-1.78	0.47			
Fundus						
Activity	2.13	1.48-3.07	<0.001	1.8	[1.01-2.95]	0.02
Density of H.Pylori	1.57	1.11-2.20	0.01	1.05	[0.67-1.66]	0.82

explain these differences across studies: like the minimal histological score chosen for considering atrophy, or the number of biopsies taken.

Furthermore, geographical factors are known to greatly influence the prevalence of premalignant lesions. Some environmental particularities could protect from the outcomes of *H. pylori* infection. For instance in Africa, one hypothesis states that helminth infection, which is very important in this region, could shift the *H. pylori*-induced Th1 pro-inflammatory response towards a Th2 response classically induced by nematode infections, neutralizing the harmful effects of the *H. pylori* infection^[11].

This hypothesis could explain on the one hand the low prevalence of gastric atrophy found in our study as well as the Tunisian study cited above; and could, on the other hand, highlights the pivotal role of the degree of inflammation in the carcinogenesis.

The study finding show that the activity of gastritis is an independent risk factor for the premalignant lesions with ORs of 2.66, 2.09 for atrophy respectively in Antrum and Fundus and 1.81 and 1,8 for intestinal metaplasia in antrum and fundus respectively. No published work has evaluated the direct relation between the activity of gastritis and those lesions. Nevertheless, our results were indirectly consistent with the results of some studies aimed at assessing the pro-inflammatory capacities of the different *H. pylori* strains^[12,13,14]. Those findings show that the differences in prevalence of gastric atrophy and intestinal metaplasia are pertained to differences among bacterial strains. As matter of fact, these lesions are more prevalent in CagA-positive *H. pylori* infected patients; histologically these strains are known to be associated with high score of mononuclear cell and polymorphonuclear cell infiltration, which defines a high activity of gastritis. These results are in agreement with the findings of Figueiredo *et al*^[15]. In his study, he has shown that vacAs1-, vacAm1-, and cagA-positive *H. pylori* strains have pro-inflammatory properties, and moreover they are associated with increased risk of GC. According to the same study, the inflammatory response depends on the immunology of the host. GC and premalignant lesions resulted in hypochlorhydria in patients with an immunogenotype of TH1, IL1, TNF-like pro-inflammatory cytokines. The association of a pro-inflammatory genotype with vacAs1-, vacAm1-, and cagA-positive *H. pylori* strains increases the risk of cancer compared to the general population with ORs of 87, 7.4, and 25, respectively. These results provide evidence that the degree of inflammation and therefore the activity of gastritis is a predisposing factor to premalignant lesions.

Despite the studies that have been conducted in this context; the mechanisms leading premalignant lesions remain unclear. However, it is hypothesized that virulent strains of *H. pylori* trigger a pro-inflammatory immune response, producing IL-1 β , TNF and IL-8. This inflammatory response may fail to eliminate the bacteria and chronic infection occurs. The increased in chemokine production, principally the Tumor Necrosis Factor (TNF) induces cellular damage and apoptosis, which could promote development of atrophic gastritis^[16].

Many studies evaluates the dynamics of atrophy and intestinal metaplasia after *H. pylori* eradication. In the stage of chronic gastritis, bacterial eradication is accompanied by the the regression of polymorphonuclear cells in a few days and the regression of the lympho-plasmocytic infiltration with restoration of a normal gastric mucosa in a few months. In the following stages, although the eradication of the *H. pylori* infection could stop the extension of gastric atrophy and intestinal metaplasia, premalignant lesions seems to be "a point of no return" and are, therefore, unlikely to regress after the eradication^[17].

CONCLUSION

In this series of patients, the prevalence of gastric atrophy and intestinal metaplasia were 12.6% and 7.7% respectively; these values are low compared to what has been reported in other series. We, furthermore demonstrated in agreement with data of literature, that the activity of gastritis in the antrum is a predictive factor of these lesions.

Evidence shows that the process of gastric carcinogenesis is a multifactorial event involving permissive environmental factors and genetically susceptibility. However, *H. pylori* infection triggers the carcinogenesis cascade. Which led several open-label trials and meta-analyses to support the chemopreventive effect of *H. pylori* eradication on gastric cancer.

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