

Prevalence of *H.pylori* Infection and Precancerous Gastric Lesion in Family Relative of Gastric Cancer in South West of Iran

Masjedizadeh AR, Fathizadeh P, Shayesteh AA, Alavinejad P, Hashemi J, Hajiani E

Masjedizadeh AR, Fathizadeh P, Shayesteh AA, Alavinejad P, Hashemi J, Hajiani E, Research institute for infectious diseases of digestive system, School of Medicine, Ahvaz Jundi Shapur University of Medical Sciences, Ahvaz, Iran

Correspondence to: Abdol Rahim Masjedizadeh, Deivision of Gastroenterology and Hepatology, Department of Internal Medicine, Ahvaz Jundishpur University of Medical Sciences, Emam Hospital, P.O. Box 89, Ahvaz, Iran. rahim.masjedi@gmail.com

Telephone: +989161114970

Fax: +986113910642

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ABSTRACT

AIM: Progression of *Helicobacter Pylori*-associated gastritis is a major pathway for development of gastric adenocarcinoma. A family history of gastric adenocarcinoma has been demonstrated in some studies. The aim of this study was to assess the prevalence of precancerous gastric lesions in first-degree relative of gastric adenocarcinoma patients.

METHODS: After gastric adenocarcinoma was histologically confirmed in a patient, the first-degree relatives were invited to participate in the study and underwent gastric endoscopy and biopsy. The control group was comprised of individuals who underwent endoscopic retrograde cholangiopancreatography (ERCP), in whom there were no evidence of peptic ulcer and no family history of gastric adenocarcinoma. A total of six gastric biopsies were taken and studied: two from the antrum, two from corpus, and two from cardia. Histologic examinations were performed separately by three board-certified pathologists and reported according to the updated Sydney system.

RESULTS: 184 individuals were included in the study, including 92 in the study group and 92 in the control group. The mean age was similar between two groups (40.75±9.5 and 40.39±11 years of age, respectively). 57.6% of the control group and 52.4% in the study group were above the age of 40. Study group showed a higher prevalence of *H. pylori* (HP) infection in the body and cardia, comparing to the control group (73.9% and 75% vs 58.7% and 57.8%; $P=0.01$ and 0.04). There was no statistically significant difference in the prevalence of antral HP infection between the two groups (70.7% vs. 58.7%; $P=0.06$). HP

density showed similar difference between the two groups ($P=0.01$, $P=0.04$ vs $P=0.06$). There is significant difference between two groups in Severity of the neutrophilic infiltration in antrum, body and cardia. ($P=0.004$, $P=0.001$, $P=0.01$ respectively). Severity of lymphoid aggregate in the study group was greater in the antrum than of the body and cardia. ($P=0.0001$ vs $P=0.22$ and $P=0.75$). Study group showed higher prevalence of HP-associated chronic gastritis in antrum, body and cardia (48.9%, 44% and 38% vs 30.4%, 23.9%, 22.8%; $P=0$). Frequency of antral, body and cardia HP infection in the background of intestinal metaplasia (IM) was similar in the two groups (7%, 4%, 4% vs 9%, 3% and 9%; $P=0.74$, $P=0.99$, $P=0.46$). Prevalence of HP-associated dysplasia between study and control groups in the antrum, body, and cardia, were respectively (15%, 16%, 12% vs 13%, 5%, 18% $P=0.78$, $P=0.07$, $P=0.91$).

CONCLUSION: Screening for HP infection and precancerous lesions may provide a preventive way for development of gastric adenocarcinoma

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Key words: Gastric adenocarcinoma; First-degree relatives of gastric cancer patients; Precancerous gastric lesions; *Helicobacter Pylori*; Atrophic gastritis; Intestinal metaplasia; Dysplasia

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INTRODUCTION

Gastric adenocarcinoma is a common malignancy worldwide; however, its incidence varies greatly in different geographic areas^[1]. In Iran, Northern and Northwestern regions show the highest prevalence. The incidence of gastric adenocarcinoma for men and women, with an age standardized incidence rate (ASR), are approximately 49.1 and 25.4 per 100000 person-years, respectively^[2,3]. Premalignant gastric lesions are well known risk factors for the development of intestinal-type gastric

adenocarcinoma^[4]. In a multistep cascade, chronic *Helicobacter Pylori* (HP)-induced gastritis progresses through premalignant stages of intestinal metaplasia (IM), atrophic gastritis (AG), and dysplasia, to eventually gastric adenocarcinoma^[5]. Therefore, this multi-step process may provide a basis for early detection and treatment of gastric adenocarcinoma. The prevalence of premalignant gastric lesions show considerable geographic variation, and is clearly associated with the regional prevalence of HP infection^[6]. In Iran, HP infection has been reported in over 89% of the adults over 40 year of age; however, this rate varies in different regions of the country^[7]. AG is present in 45%, 47%, and 22% of gastric antral, body and cardiac biopsies, respectively. IM is present in 47% of individuals with gastric adenocarcinoma and 11% of non-ulcer dyspepsia^[8]. Nonetheless, some reports describe certain regions with a high prevalence of HP infection, yet low prevalence of gastric adenocarcinoma and precursor lesions^[9]. Therefore, other factors such as diet, HP strain and the host immune response may also contribute to the geographic variation of gastric adenocarcinoma prevalence and its precursors. Large epidemiologic studies on the relatives of gastric adenocarcinoma patients show significant increased risk associated with diffuse-type carcinoma and a slight increase risk associated with intestinal-type gastric adenocarcinoma^[10]. In addition, relatives of gastric adenocarcinoma patients have an increased prevalence of premalignant gastric lesions comparing to the matched control groups^[11]. To what extent this risk is independent from HP infection status is yet to be determined.

The value of screening asymptomatic first-degree relative of gastric adenocarcinoma patients is a controversial issue. The potential benefit of surveillance has been evaluated in a few studies. The aim of this study was to assess histopathologic patterns of gastritis and prevalence of precursor lesions in the first-degree relative of gastric adenocarcinoma in a population with high incidence of gastric adenocarcinoma.

METHODS

This study was approved by ethnical and research committee of Jundishapour University of Medical Sciences (establishing No. 73).

First-degree relatives of gastric cancer patients were invited to our meetings. They were educated about the gastric adenocarcinoma, its prevalence in Iran, course of changes form precursor gastric changes to gastric adenocarcinoma, possible family risk factors and our study goals. After informed consent, one or two first-degree relatives were enrolled the study groups. The volunteers were between eighteen to sixty-five years of age.

Exclusion criteria were history of peptic ulcer, finding ulcer during endoscopy, history of gastric surgery, history of GI malignancy, consumption of PPI or H2 blocker and consumption of antibiotics in the past four weeks.

Results of endoscopy and biopsy of this population were compared by age and gender-matched control group. The control group

individuals were selected from ERCP candidates for biliary stones with normal esophagogastroduodenoscopy findings.

Histological assessment

2 samples from antrum, 2 to 3 cm above pylorus, 2 samples from body and 2 samples from cardia were taken. The biopsies were submitted in separate containers in 10% buffered formalin. After routine histology processing, H&E (hematoxylin and eosin) stained sections were prepared for routine examination. Toluidine Blue stain was used to highlight HP organisms. The histologic findings were examined and reported separately by 3 board-certified pathologists based on updated Sydney system. Pathologists were not provided any clinical or endoscopy information.

Statistical Analysis

The pathology reports findings based on the updated Sydney system were compared between the two groups using SPSS software with student *t*-test (X^2) and Fischer extraction test.

The difference between data between two groups were compared by Mann-Whitney U-test. *P* values<0.05 were considered statistically significant

RESULTS

Totally 184 individuals were studied. 92 first-degree relatives of gastric adenocarcinoma patients were studied in comparison to the 92 age-matched and gender-matched individuals in control group. Mean ages in study and control groups were 40.7±9.5 and 40.36±11, respectively.

57.6% of the study group and 52.2% of the control group were older than 40 years of age.

57.6% of the study group and 60.9% of the control group were female.

Study group showed higher prevalence of HP infection in antrum, body and cardia (70.7%, 75% and 73.9% vs 58.7%, 58.7% and 57.8%; *P*=0.01, *P*=0.04, *P*=0.04).

Study group also showed higher HP density in body and cardia, but not antrum (*P*=0.01, *P*=0.04 and *P*= 0.06) (Table 1).

Study group showed higher prevalence of neutrophilic infiltration in the antrum, body and cardia (*P*=0.004, *P*=0.001, *P*=0.01) and rate of lymphoid aggregation was significant in antrum in study group. (*P*=0.0001). There was no statistical significance in the antrum, body and cardia regions in plasmacytic infiltration between groups. (*P*=0.3, *P*=0.19 and *P*= 0.09) (Table 2).

HP-associated chronic gastritis was more prevalent in the study group (48.9%, 44% and 38% vs 30.4%, 23.9%, 22.8%). Overall HP-

Table 1 *H. Pylori* infection prevalence.

	Antrum (%)	Body (%)	Cardia (%)
Study group	70.7	73.9	75
Control Group	58.7	58.7	57.8
<i>P</i> Value	0.06	0.01	0.04

Table 2 The grade of plasmacytic infiltration, neutrophilic infiltration, and lymphoid aggregation in studied groups (%).

	Plasmacytic infiltration				Total <i>P</i>	Neutrophilic infiltration				Total <i>P</i>	lymphoid aggregation		Total <i>P</i>			
	Inactive	Mild	Moderate	Severe		Inactive	Mild	Moderate	Severe		Inactive	Mild				
Antrum																
Study relatives	5 (5.5%)	32 (34.7%)	53 (57.6%)	2 (2.2%)	92	0.3	45 (48.9%)	42 (45.6%)	5 (5.5%)	0 (0)	92	0.004	45 (48.9%)	42 (45.6%)	92	0.004
Control group	9 (9.8%)	27 (29.4%)	56 (60.8%)	0 (0)	92		66 (71.7%)	25 (27.1%)	1 (1.2%)	0 (0)	92		66 (71.7%)	25 (27.1%)	92	
Corpus																
Study relatives	4 (4.4%)	30 (32.6%)	58 (63%)	0 (0)	92	0.19	46 (50%)	39 (42.4%)	7 (7.6%)	0 (0)	92	0.001	46 (50%)	39 (42.4%)	92	0.001
Control group	10 (11%)	32 (34.7%)	50 (54.3%)	0 (0)	92		70 (76.1%)	19 (20.6%)	3 (3.3%)	0 (0)	92		70 (76.1%)	19 (20.6%)	92	
Cardia																
Study relatives	3 (3.3%)	37 (40.2%)	52 (56.5%)	0 (0)	92	0.09	55 (59.7%)	28 (30.4%)	9 (9.9%)	0 (0)	92	0.01	55 (59.7%)	28 (30.4%)	92	0.01
Control group	10 (10.9%)	39 (42.3%)	43 (46.8%)	0 (0)	92		73 (79.3%)	12 (13.1%)	7 (7.6%)	0 (0)	92		73 (79.3%)	12 (13.1%)	92	

associated chronic gastritis was more prevalent in the study group ($P=0.001$).

The two groups showed similar prevalence of HP-associated IM. Nevertheless, control group showed a higher prevalence of HP-negative IM in the body. ($P= 0.038$)(Table 3).

There was no difference between study and control groups in HP-associated dysplasia and Dysplasia in the absence of HP infection. (Table 4).

DISCUSSION

Gastric adenocarcinoma is a multifactorial disease. Environmental factors such as HP infection and diet are believed to be major contributors to gastric carcinogenesis, but host factors have also been implicated. Helicobacter and Cancer Collaborative Group have demonstrated relationship of HP infection and gastric adenocarcinoma in a meta-analysis of 12 case-control studies^[12]. Average prevalence of HP infection in developed countries (low-risk for gastric adenocarcinoma and developing countries (high-risk for gastric adenocarcinoma) are 35% and 85%, respectively^[13]. Fock KM *et al* showed that approximately 65% and 80% of non-cardia gastric adenocarcinomas were attributable to HP infection and potentially preventable^[13]. It is clear that those countries with high gastric adenocarcinoma ASR have a high seroprevalence of HP infection. There are also populations with a high seroprevalence of HP infection but a purportedly low gastric adenocarcinoma, such as India and Thailand^[14]. This may be probably related to host genetic factors, bacterial virulence and environmental factors. Approximately 80% of histologically proven HP-associated gastritis patients are asymptomatic^[15]. A body of evidence supports the role of host factors in progression of HP-associated gastritis to gastric adenocarcinoma. The risk of gastric adenocarcinoma is increased up to three-folds in first-degree relatives of these patients, and 10% gastric adenocarcinomas show familial clustering^[16]. It has been demonstrated that first-degree relatives of patients with gastric adenocarcinoma have a higher prevalence of gastric atrophy and hypochlorhydria in a back ground of HP-associated gastritis^[17]. Among populations with high prevalence of HP infection cagA-positive strains area associated with an increased overall risk of

gastric adenocarcinoma 1.6-fold (95% CI: 1.2-2.2) and of non-cardia gastric adenocarcinoma 2.0-fold (95% CI: 1.2-3.3)^[18]. Cardia-type gastric adenocarcinoma has not been shown to be associated with HP infection or cagA positive strains of HP^[19]. Prevalence of cagA stains of HP in Asia is high; however, the current cagA genotypes in the Asia-Pacific region are not associated with GA. Recently we studied the relationship between serum pepsinogens and *Helicobacter Pylori* cag-A status and precancerous gastric lesions. In that study,we showed that the mean level of pepsinogen-I was 93.15 ± 61.06 and this value was not statistically significantly related to CagA and *H. pylori* status ($P>0.05$).The mean level of pepsinogen-II was 14.46 ± 12.58 which was not associated with *H. pylori* and CagA status again than ($P=0.98$ and $P=0.058$ respectively)^[20].

The sequence of HP infection, gastritis, gastric atrophy, IM, dysplasia and adenocarcinoma is well known. In high-risk regions of the world for gastric adenocarcinoma, there is a pressing need for preventive policies. Such policies have been established in certain parts of the world such as Japan, Korea and Taiwan^[21,22]. In Japan, screening with double-contrast barium or endoscopy is offered after the age of 40^[23]. In Korea, endoscopy is used, while in Taiwan, screening is in two steps starting with serum pepsinogen level, based on which endoscopy is performed^[11].

El Omar *et al* examined the prevalence of gastric atrophy and hypochlorhydria and their association with HP infection in the first-degree relatives of patients with gastric adenocarcinoma^[24]. They found that among the first-degree relatives of gastric adenocarcinoma patients, the prevalence of gastric atrophy and hypochlorhydria was increased only in those with evidence of HP infection^[25]. In our study, the prevalence of HP infection in body and cardia in the study group was higher than the control group. (73.9%, 75% vs 58.7%, 58.7%) ($P=0.01$ and $P=0.04$). There was no statistically significant difference in the antrum (70.7% vs 57.8%; $P=0.6$). Motta CR and Antonia R showed higher prevalence of HP in the relatives of GA patients (84.7% and 85.7%)^[26,27]. Similar to our study, they found a higher HP density in the body and cardia of the family group ($P=0.01$, $P=0.04$), with no statistically significant difference in antral region ($P=0.6$). In their study HP density in all three regions of the stomach was higher in the family group. The

Table 3 Rates of intestinal metaplasia in study and control groups with and without *H. pylori* infection.

<i>Helicobacter pylori</i>	Study group			Control group			P
	Intestinal metaplasia	Total		Intestinal metaplasia	Total		
Antrum	Pos	Neg		Pos	Neg		
Positive	5 (7%)	63 (93%)	68 (100%)	5 (9%)	49 (91%)	54 (100%)	0.74
Negative	2 (9%)	22 (91%)	24 (100%)	2 (5%)	36 (95%)	38 (100%)	0.63
Body							
Positive	3 (4%)	66 (96%)	69 (100%)	2 (3%)	52 (97%)	54 (100%)	0.99
Negative	0 (0%)	23 (100%)	23 (100%)	7 (18%)	31 (82%)	38 (100%)	0.038 ¹
Cardia							
Positive	3 (4%)	65 (96%)	68 (100%)	5 (9%)	49 (91%)	54 (100%)	0.46
Negative	1 (4%)	23 (96%)	24 (100%)	2 (5%)	36 (95%)	38 (100%)	0.99

¹p value more than 0.05 is significant.

Table 4 Rates of Dysplasia in study and control groups with and without *H. pylori* infection .

<i>Helicobacter pylori</i>	Study group			Control group			P
	Dysplasia	Total		Dysplasia	Total		
Antrum	Pos	Neg		Pos	Neg		
Positive	10 (15%)	58 (85%)	68 (100%)	7 (13%)	47 (87%)	54 (100%)	0.78
Negative	1 (4%)	23 (96%)	24 (100%)	0 (0%)	38 (100%)	38 (100%)	0.38
Corpus							
Positive	11 (16%)	58 (84%)	69 (100%)	3 (5%)	51 (95%)	54 (100%)	0.07
Negative	0 (0%)	23 (100%)	23 (100%)	1 (2%)	37 (98%)	38 (100%)	0.99
Cardia							
Positive	8 (12%)	60 (88%)	68 (100%)	6 (18%)	48 (82%)	54 (100%)	0.91
Negative	0 (0%)	24 (100%)	24 (100%)	5 (13%)	33 (87%)	38 (100%)	0.14

inflammatory response in the family group, including mononuclear cell infiltration, lymphoid aggregates and polymorphonuclear cell infiltration were all more pronounced in the gastric body ($P=0.03$). The inflammatory response in the antrum and cardia was not higher in the family group ($P=0.25$, $P=0.2$). In our study HP-associated chronic gastritis was more common in all three regions in control group (48.9%, 44%, 38% vs 30.4%, 23.9%, 22.8%; $P=0$). In addition, neutrophilic infiltration in the antrum, body and cardia ($P=0.004$, $P=0.001$, $P=0.01$) and rate of lymphoid aggregation was significant in antrum in study group. ($P=0.0001$). In another study by Adriana Romiti and et al, 39 first-degree relatives of gastric cancer patients and 39 matched controls were evaluate gastric epithelial cell proliferation values were not significantly different between the patient and control groups. ($P=0.3$). *H. pylori* infection was detected in 19 (48.7%) of these patients. Chronic active gastritis was observed in all the infected patients, whilst it was absent in the remaining 20 uninfected patients. Intestinal metaplasia was present in 14 out of 39 patients (35.8%), being significantly more frequent in patients with *H. pylori* infection than in uninfected patients ($P=0.037$)^[28].

In our study, HP-associated IM was similarly common in the study and the control group (7%, 4%, 4% vs 9%, 3%, 9%; $P=0.74$, $P=0.99$, $P=0.46$ in antrum, body and cardia. We couldn't find any difference between two groups in HP-associated dysplasia. ($P=0.78$, $P=0.07$, $P=0.91$). in contrary, Motta CR shows that intestinal metaplasia located in the body was significantly more frequent in the gastric cancer relatives than in the controls^[27] ($P=0.04$). The prevalence of dysplasia was 7.1% in the cancer relative group compared with 0.8% in the control group ($P=0.03$)^[27].

CONCLUSION

Although the rate of intestinal metaplasia and dysplasia in both groups had not showed any differences in this study, the rate of chronic gastritis and *H.pylori* infection in first-degree relatives of gastric cancer patients is an address for the screen of this group.

REFERENCES

- Sasako M, Inoue M, Lin JT, Khor C, Yang HK, Ohtsu A. Gastric cancer working group report. *Jpn J Clin Oncol* 2010; **40** (Suppl 1): 28-37
- Salehi Z, Mollasalehi H, Jelodar MH, Kazemi M, Zahmatkesh R. The relationship between *Helicobacter Pylori* infection and gastric adenocarcinoma in Northern Iran. *Oncol Res* 2010; **18**(7): 323-328
- Malekzadeh R, Derakhshan MH, Malekzadeh Z. Gastric cancer in Iran: Epidemiology and risk factors. *Arch Iran Med*. 2009; **12**(6): 576-583
- Correa P, Houghton J. Carcinogenesis of *Helicobacter Pylori*. *Gastroenterology* 2007; **133**(2): 659-672
- Muller LB, Fagundes RB, Moraes CC, Rampazzo A. Prevalence of *Helicobacter Pylori* infection and gastric cancer precursor lesions in patients with dyspepsia. *Arq Gastroenterol* 2007; **44**(2): 93-98
- Hussein NR. *Helicobacter Pylori* and gastric cancer in the Middle East: a new enigma. *World J Gastroenterol* 2010; **16**(26): 3226-3234
- Miwa H, Go ME, Sato N. *H. pylori* and gastric cancer: the Asian enigma. *Am J Gastroenterol* 2002; **97**: 1106-1112
- Weck MN, Brenner H. Prevalence of chronic atrophic gastritis in different parts of the world. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 1083-1094
- Chacaltana A, Rodríguez C, Urday C, Ramon W, Espinoza J, Velarde H, Rodríguez I, Lucho E, Rauch E. Preneoplastic gastric lesions and *Helicobacter Pylori* in endoscopic detection and early diagnosis of gastric cancer in a population of a medium and high socio-economic level. *Rev Gastroenterol Peru* 2009; **3**: 218-225
- Nam JH, Choi IJ, Cho SJ, Kim CG, Lee JY, Nam SY, Park SR, Kook MC, Nam BH, Kim YW. *Helicobacter Pylori* infection and histological changes in siblings of young gastric cancer patients. *J Gastroenterol Hepatol* 2011; **26**(7): 1157-1163
- El-Omar EM, Oien K, Murray LS, El-Nujumi A, Wirz A, Gillen D, Williams C, Fullarton G, McColl KE. Increased prevalence of precancerous changes in relatives of gastric cancer patients: critical role of *H. pylori*. *Gastroenterology* 2000; **118**(1): 22-30
- Helicobacter, Cancer Collaborative G. Gastric cancer and *Helicobacter Pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001; **49**(3): 347-353
- Fock KM, Ang TL. Epidemiology of *Helicobacter Pylori* infection and gastric cancer in Asia. *J Gastroenterol Hepatol* 2010; **25**(3): 479-486
- Azuma T, Yamazaki S, Yamakawa A, Ohtani M, Muramatsu A, Suto H, Ito Y, Dojo M, Yamazaki Y, Kuriyama M, Keida Y, Higashi H, Hatakeyama M. Association between diversity in the Src homology 2 domain-containing tyrosine phosphatase binding site of *Helicobacter Pylori* CagA protein and gastric atrophy and cancer. *J Infect Dis* 2004; **189**: 820-827
- Fox JG, Wang TC. Inflammation, atrophy, and gastric cancer. *J Clin Invest* 2007; **117**: 60-69
- Leung WK, Ng EK, Chan WY, Auyeung AC, Chan KF, Lam CC, Chan FK, Lau JY, Sung JJ. Risk factors associated with the development of intestinal metaplasia in first-degree relatives of gastric cancer patients. *Cancer Epidemiol Biomarkers Prev* 2005; **14**(12): 2982-2986
- Adamu MA, Weck MN, Gao L, Brenner H. Incidence of chronic atrophic gastritis: systematic review and meta-analysis of follow-up studies. *Eur J Epidemiol* 2010; **25**(7): 439-448
- Huang JQ, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. Meta-analysis of the relationship between caga seropositivity and gastric cancer. *Gastroenterology* 2003; **125**: 1636-1644
- Wen S, Moss SF. *Helicobacter Pylori* virulence factors in gastric carcinogenesis: Review. *Cancer Lett* 2009; **282**(1): 1-8
- Masjedizadeh AR, Hajiani E, Alavinejad P, Hashemi J, Shayesteh AA, Zarkami T. Diagnostic Value of Pepsinogen I and II for Pre-cancerous Gastric Lesions in Dyspeptic Patients. *Journal of GHR* 2013; **2**(1): 369-373
- Liu CY, Wu CY, Lin JT, Lee YC, Yen AM, Chen TH. Multistate and multifactorial progression of gastric cancer: results from community-based mass screening for gastric cancer. *J MedScreen* 2006; **13**(Suppl.1): S2-5
- Kim YS, Park HA, Kim BS, Yook JH, Lee MS. Efficacy of screening for gastric cancer in a Korean adult population: a case-control study. *J Korean Med Sci* 2000; **15**: 510-515
- Yamada S, Matsuhisa T, Makonkawkeyoon L, Chaidatch S, Kato S, Matsukura N. *Helicobacter Pylori* infection in combination with the serum pepsinogen I/II ratio and interleukin-1beta-511 polymorphisms are independent risk factors for gastric cancer in Thais. *Gastroenterology* 2006; **41**: 1169-1177
- Brenner H, Arndt V, Stürmer T, Stegmaier C, Ziegler H, Dhom G. Individual and joint contribution of family history and *Helicobacter Pylori* infection to the risk of gastric carcinoma. *Cancer Epidemiol Biomarkers Prev* 2000; **88**: 274-279
- Zanghieri G, Di Gregorio C, Sacchetti C, et al. Familial occurrence of gastric cancer in the 2-year experience of a

- population-based registry. *Cancer Epidemiol Biomarkers Prev* 1990; **66**: 2047-2051
- 26 Sepulveda A, Peterson LE, Shelton J, Gutierrez O, Graham DY. Histological Patterns of Gastritis in *H. pylori*-Infected Individuals With a Family History of Gastric Cancer. *Am J Gastroenterol* 2002; **97(6)**: 1365-1370
- 27 Motta CR, Cunha MP, Queiroz DM, Cruz FW, Guerra EJ, Mota RM, Braga LL. Gastric Precancerous Lesions and *Helicobacter Pylori* Infection in Relatives of Gastric Cancer Patients from Northeastern Brazil. *Digestion* 2008; **78**: 3-8
- 28 Romiti A, Zullo A, Tomao S, Hassan C, Sarcina I, De

Francesco V, Ierardi E, Tomao F, Vecchione A, Morini S. Gastric mucosa alterations in first-degree relatives of gastric cancer patients. *Anticancer Res* 2005; **25(3c)**: 2567-2572

Peer reviewers: Geng ming, Department of Pathology, General Hospital of Jinan Military Command, 25#, Shifan Road, Jinan, 250031, Province of Shandong, China; Rommel Burbano, Laboratório de Citogenética Humana, Instituto de Ciências Biológicas, Campus Universitário do Guamá/ Universidade Federal do Pará, Av. Augusto Correa, 01, CEP 66075-110, Belém, Pará, Brazil.