RESEARCH COMMUNICATION

Gastric Precancerous Lesions in First Degree Relatives of Patients with Known Gastric Cancer: a Cross-Sectional Prospective Study in Guilan Province, North of Iran

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Abstract

Background & Objectives: In patients with gastric cancer, the most frequently reported family history of cancer also involves the stomach. The aim of this study was to assess the presence of gastric precancerous lesions in first-degree relatives of patients with gastric cancer and to compare the obtained results with those of individuals with no such family history. Methods: Between 2007 and 2009, 503 consecutive persons more than 30 years old were enrolled in the study covering siblings, parents or children of patients with confirmed adenocarcinoma of stomach. The control group was made up of 592 patients who were synchronously undergoing upper gastrointestinal endoscopy for evaluation of dyspepsia without gastric cancer or any family history. All subjects were endoscopically examined. Results: The overall prevalence of *Helicobacter pylori* was 77.7% in the cancer relatives and in 75.7% in the control group. Chronic gastritis was found in 90.4% vs. 81.1% (P<0.001). Regarding histological findings, 37(7.4%) of the study group had atrophy vs. 12(1.7%) in the control group (P<0.001), while no difference was observed for intestinal metaplasia (20.3% vs. 21.6%, P=0.58). Dysplasia were shown in 4% of cancer relatives but only 0.4% of the control group (P<0.001). There was no gender specificity. Conclusions: Findings of our study point to great importance of screening in relatives of gastric cancer patients in Iran.

Keywords: Gastric cancer - relatives - Guilan - Iran - screening

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Introduction

Gastric cancer is a major public health as the fourth most common cancer and second leading cause of cancer-related death in the world (De Vries et al., 2007; Motta et al., 2008; Herszényi and Tulassay, 2010; Yaghoobi et al., 2010). According to recent studies, about 7300 cases in Iran (10.5 per 100,000 individuals) are afflicted to gastric cancer annually (Mehrabian etal., 2010). The initial diagnosis of gastric cancer often is delayed because most patients are asymptomatic in the early stage, so unfortunately, gastric cancers are usually diagnosed at their advanced stages (Zhang et al., 2005; Mehrabian etal., 2010). In patients with gastric cancer, the most frequently reported family history of cancer is that of gastric cancer (Kawasaki et al., 2007). Estimates suggest that siblings or offspring of gastric cancer patients have at least 1.5 fold higher risk of gastric cancer (Dhillon et al., 2001; Yaghoobi et al., 2010). The odds ratio (OR) for the development of gastric cancer in patients with a family history of gastric cancer has been reported to be 1.6-2.6 (Kondo et al., 2003; Kawasaki et al., 2007). Genetic, epigenetic and environmental factors are all considered to be great contributors to such an increased risk (Niv et al., 2003; Herszényi and Tulassay, 2010; Nadauld and Ford, 2012).

In Iran especially in Guilan province, gastric cancer is the most common form of cancer (Malekzadeh et al., 2009). Despite the fact that the risk of developing gastric cancer is much higher in relatives of patients with a positive family history (Brenner et al., 2000; Dhillon et al., 2001; Chang et al., 2002; Nadauld and Ford, 2012), not much data is available on familial predisposition to the gastric cancer precursor state and their transitions from less to more advanced lesions. Also there isn't any data about comparing relatives of gastric cancer patients with healthy individuals (Motta et al., 2008). Therefore, we conducted a cross-sectional study to evaluate the presence of gastric precancerous lesions in relatives of gastric cancer patients and to compare with individuals with no family history of gastric cancer in Guilan province, north of Iran.

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Materials and Methods

An informed consent was obtained from each person prior his/her participation. Those without inform consent were taken apart. The study protocol was approved by the clinical research ethics committee of Gastrointestinal and Liver disease research center (GLDRC) of Guilan University of Medical Sciences (GUMS). Between April 2007 and April 2009, 503 consecutive person more than 30 years old were enrolled the study consist of siblings, parents or children of patients with confirmed adenocarcinoma of stomach. A control group was made up of 592 patients who were synchronously undergoing upper gastrointestinal (GI) endoscopy for evaluation of dyspepsia. They have no gastric cancer or family history of gastric cancer. Both case and control groups were match for age and sex. For all the patients, detailed information included demographic data, past medical illness, family history, childhood living conditions were collected. Exclusion criteria were existence of peptic ulcer and GI bleeding in endoscopy, history of gastrectomy, cardiopulmonary failure, hepatic and renal failure, consumption of some drugs 4 weeks before endoscopy such as H2 Blocker, protein pomp inhibitors (PPIs), Sucralfat , antibiotic and Nonsteroidal anti-inflammatory drugs (NSAIDs).

Gastroscopy was performed with Olympus video endoscopes (Olympus Optical Co, Ltd, GIF type V) in the standard manner. Fragments of the gastric mucosa were obtained from the six sites: 1. antrum (site 1) for rapid urease test (RUT), Antrum lesser curve (site 2), Antrum greater curve (site 3), the angulus (site 4), the middle body (site 5) and Fondus (site 6) of the stomach. RUT was done for detection of *H.Pylori* infection. For the urease test, fragment obtained from the antral mucosa of the stomach was placed in a tube containing Christensen's 2% urea agar to detect performed ureas that examined within 24 h of incubation at 37 °C. *H. pylori* status was identified by the rapid urease test and by histology through Giemsa staining. If both tests are negative *H.pylori* status will be negative. Gatric biopsy specimens were fixed in 10% buffered formalin and embedded in paraffin, and 5-mm formalin fixed tissue were stained with hematoxylin and eosin and with Giemsa stain to recognize *H. pylori* density. Biopsy specimens were evaluated and reviewed by a single, blinded expert pathologist.

Histological classification of gastric cancer type was based upon Sydney System (Sepulveda et al., 2002; Zhang et al., 2002; Dinis-Ribeiro et al., 2012). The degree of each endoscopic finding was graded from 0 (absent/normal) to 3 (maximal intensity). We survived some parameters such as activity, inflammation, glandular atrophy, intestinal metaplasia, dysplasia and density of *H. pylori* colonization. Activity, inflammation and glandular atrophy were recognized, respectively, by granulocytic infiltration, lymphocytic and plasma cells infiltration, loss of normal glands. The pattern of gastritis was determined based on the distribution of inflammation. Gastric dysplasia is a precursor lesion for gastric carcinoma for site at which it is found, it is characterized by cellular atypia, abnormalities in the differentiation of the epithelium, and disorganized architecture of the gastric foveolae and glands, but without penetration into lamina propria (Sepulveda et al., 2002).

Statistical analysis

The results for quantitative variables were expressed as mean ± standard deviation (SD), and values of the qualitative variable were represented by the percentage. The groups were compared using the Student's t- test for continuous variables and the chi-square test (or Fisher's exact test if required) for categorical variables. Statistical significance was based on two-sided design-based tests evaluated at the 0.05 level of significance. All the statistical analyses were performed using SPSS version 16 (SPSS Inc, Chicago, IL, USA) for Windows.

Results

From 2007 to 2009, 1095 persons participated in our study that 503 persons were cancer relatives and 592 persons without family history of gastric cancer were assigned as group. A significant difference was not found between cancer relatives and control group for mean age (43.4 ± 8 vs. 43.5 ± 12.4 years, P=0.8). Cases and control did not show a significant difference for marital status (P=0.21). The overall prevalence of *H.pylori* was 77.7% in the cancer patient's relatives and in 75.7% of control group and there was not a significant statistically difference between two groups (P=0.233). Patients` demographic characteristics and histopathologic findings have been summarized in Table1.

There were a significant statistically difference in chronic gastritis, atrophy and dysplasia between relatives group and control group (P<0.001). No significant statistically difference was confirmed between two studied groups for intestinal metaplasia in histological findings, (P=0.58).

In case group, no significant association was found between male gender and existence of *H. Pylori* infection (OR=1.05, 95% CI= 069-1; P= 0.79), chronic gastritis (OR=0.71, 95% CI= 0.39-1.2; P=0.26), intestinal metaplasia (OR=0.93, 95% CI=0.6 1.42; P=0.74) and dysplasia (OR=1.36, 95% CI =0.55-3.35; P=0.49).Most of the cancer relatives were in age group 40-45 years (25.8%) and the proportion of old ages (60-65 years) was not considerable (4.2%).

Among cancer relatives, most of the persons with chronic gastritis were in age range of 40-50 years old.

Table 1. Demographic and Pathologic Features of Relatives of Gastric Cancer and Control Group

Variables		Case (N=503)	Control (N=592)	P-Value
Sex	Male	239 (47.5)	302 (51)	0.12
	Female	264 (52.5)	290 (49)	
Marital status	Single	15 (3)	24 (4)	0.215
	Married	488 (97)	568 (96)	
H.pylori infection		391 (77.7)	448 (75.7)	0.96
Chronic g astritis		454 (90.4)	480 (81.1)	<0.001
Atrophy		37 (7.4)	10 (1.7)	<0.001
Dysplasia		20 (4.0)	2 (0.4)	<0.001
Intestinal metaplasia		102 (20.3)	127 (21.6)	0.58

Abnormal histological findings such as atrophy (OR=0.34, 95% CI= 0.17-68; P=0.001), Intestinal metaplasia (OR=0.44, 95% CI= 0.28-68; P=0.000) and dysplasia (P=0.01) (OR=0.35, 95% CI= 0.14-87; P=0.019) were more common in ages > 46 years compared to ≤ 45 years. Our data have speculated that most types of histologic features were more prevalent in 40-49 years old.

Discussion

Gastric cancer is one of the most common and lethal cancers in Iran (Malekzadeh et al., 2009; Mehrabian etal., 2010). Unfortunately, at least 80% of Iranian patients with gastric cancer are usually diagnosed in advanced stages of the disease and they do not get any survival benefit treatment modalities (Malekzadeh et al., 2009; Mehrabian etal., 2010). Adenocarcinomas develop through a series of sequential precancerous lesions in the gastric mucosa. Prevention of gastric cancer precursor lesions progression to carcinoma and detection of cancer in an earlier stage is the main goal. On the other hand, effects of environment on familial gastric cancer are not understood clearly and little is known about events which predispose a relative to gastric cancer (Zhang et al., 2005). The purpose of this study was to assess the prevalence of gastric precancerous lesions in first-degree relatives of gastric cancer patients and to compare the results with those observed in a control group.

Guilan province is considered a high prevalence area for gastric cancer in Iran, the prevalence of *H.Pylori* infection in our study was 78%, and this prevalence is more than what found in a large study in Netherlands (De Vries et al., 2007). *Helicobacter pylori* is a well-established risk factor for gastric cancer. Previous studies have shown that individuals infected with *H. pylori* compared to non-infected individuals have more than twice as much risk of developing gastric cancer (Huang et al.,1998; Motta et al., 2008; Lee eta l., 2012). Uemura et al. (2001) found that all of the patients with gastric cancer had *H.Pylori* infection in the past. In our study, the prevalence of *H. pylori* infection among cancer patients` relatives was higher than controls, but without a statistically significant difference; maybe due to the high prevalence of *H.pylori* infection in Iranian society (Brenner et al., 2000; El-Omar et al., 2000; Malekzadeh et al., 2001).

In a study by Kawasaki et al (2007) on 440 gastric cancer patients, it was illustrated that gastric cancer was the most common familial cancer which is more common in first sibling. Although there have been a variety number of known predisposing factors for gastric cancer, a specific test improving early diagnosis has not been introduced. The relatives of gastric cancer patients were found to have a three-fold increased risk of developing gastric carcinoma (Zhang et al., 2005; Kang et al., 2011). Upper GI endoscopy and biopsy for diagnosis of precancerous lesion is relatively accounted as an appropriate method (Uemura et al., 2001; Dinis-Ribeiro etal., 2012). Our results confirmed that precancerous lesions such as dysplasia, atrophy and chronic gastritis were significantly higher in gastric cancer relatives rather than control group. Our study revealed that relatives of patients with gastric cancer developed precancerous lesions such as intestinal metaplasia, chronic gastritis and dysplasia more than those with no family history of cancer. It also points to an effect of genetic susceptibility traits in gastric cancer.

This study shows that pre-malignant gastric lesions are commonly found in routine biopsies obtained during upper GI endoscopies in Guilan province population. Atrophic gastritis is the most common premalignant condition, which is characterized by chronic inflammation of stomach mucosa with loss of gastric glandular cells and eventual replacement by intestinal and fibrous tissues. The strong points of our survey are the prospective study, the large sample size and sites evaluated in the stomach. Further longitudinal studies are suggested to assess the predisposing factors to progress precancerous lesions to malignant carcinoma in patients with a positive family history of gastric carcinoma compared to a control group.

Precancerous lesions such as dysplasia, atrophy and chronic gastritis were significantly higher in gastric cancer relatives rather than control group. It is recommended to screen individual with a family history of gastric cancer for *H. pylori* infection and gastric precancerous lesions.

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