Short Communication

Risk Factors Associated with the Development of Intestinal Metaplasia in First-Degree Relatives of Gastric Cancer Patients

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Abstract

Family relatives of gastric cancer patients have a higher risk of gastric cancer and premalignant gastric lesions. We sought to determine the risk factors associated with the presence of intestinal metaplasia in a large cohort of gastric cancer relatives. First-degree relatives of gastric cancer patients were invited for screening gastroscopy. Endoscopic gastric biopsies were obtained from the antrum and corpus. Gastric biopsies were analyzed for *Helicobacter pylori* infection, severity of inflammation, and presence of intestinal metaplasia. Stepwise logistic regressions were used to identify for risk factors associated with presence of intestinal metaplasia in cancer relatives. Two hundred seventy cancer relatives underwent screening endoscopy (median age, 42; 47% male and 48% siblings). Among them, 161 (59.6%) were *H. pylori* positive and 81 (30%) had confirmed intestinal metaplasia. The following factors were found to be associated with the presence of intestinal metaplasia: age, male sex, *H. pylori* infection, birth order, alcohol use, siblings with stomach cancer, childhood living conditions, and water supply. Individuals with intestinal metaplasia had more severe acute and chronic inflammation in the antrum and corpus ($P < 0.003$). With multiple logistic regression, *H. pylori* infection [odds ratio (OR), 3.23], male gender (OR, 2.09), age (OR, 1.07), and a history of gastric cancer in siblings (OR, 1.91) were independent factors associated with the development of intestinal metaplasia in cancer relatives. In conclusion, we have identified risk factors associated with gastric intestinal metaplasia in stomach cancer relatives, which may be useful in the understanding of gastric carcinogenesis in these high-risk individuals. (Cancer Epidemiol Biomarkers Prev 2005; 14(12):2982–6)

Introduction

Gastric cancer is the second leading cause of cancer deaths of the world (1). Despite the marked geographic variations in cancer incidence, a positive family history has been consistently shown to be a risk factor for gastric cancer in different populations (2-7). It is estimated that siblings or offspring of stomach cancer patients have at least 1.5-fold higher risk of gastric cancer (6). Apart from genetic susceptibility, the familial aggregation of gastric cancer has been attributed to common environmental factors, particularly *Helicobacter pylori* infection (5, 8, 9).

Gastric carcinogenesis is generally considered to be a multistep progression from chronic gastritis to glandular atrophy, intestinal metaplasia, dysplasia, and ultimately cancer (10). In a prospective study from Japan, *H. pylori*–infected subjects with gastric intestinal metaplasia were found to have a >6-fold increase in risk of gastric cancer (11). Changes in gastric intestinal metaplasia are therefore widely used as a surrogate end point in cancer chemoprevention trials (12-15). Notably, relatives of gastric cancer patients are also found to have a higher prevalence of gastric atrophy and hypochlorhydria in the stomach (16). The familial aggregation of gastric atrophy has again been linked to the presence of *H. pylori* infection. Unlike the interpretation of gastric atrophy, which is easily subjected to interobserver variations (17), the histologic diagnosis of intestinal metaplasia is more reliable and reproducible. Nonetheless, risk factors associated with the presence of intestinal metaplasia among family members of stomach cancer patients have not been evaluated. In this cross-sectional study, we sought to determine the risk factors associated with the presence of intestinal metaplasia in a large cohort of gastric cancer relatives.

Materials and Methods

Subjects. First-degree relatives (siblings and offspring) of patients with confirmed adenocarcinoma of stomach diagnosed in the Prince of Wales Hospital were invited to undergo upper gastrointestinal endoscopy. Relatives were excluded if they were younger than 18 or older than 75 years. Those family members who were pregnant, had previous gastric surgery, or had other serious medical conditions were excluded. Because *H. pylori* eradication therapy may interfere with the presence of intestinal metaplasia, subjects who had previously received treatment for *H. pylori* were excluded.

From July 2001 to February 2004, 270 first-degree relatives of gastric cancer patients were examined. Detailed personal and medical information that included demographic data, past medical illnesses, family history, childhood living conditions, and smoking and drinking habits were collected. The study

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protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All family members gave informed consent for participation into this study.

Endoscopy. Upper gastrointestinal endoscopy was done after an overnight fast and under conscious sedation in all relatives. Endoscopic findings were recorded and gastric biopsies were taken from the antrum and corpus according to a standard protocol. Briefly, four antral biopsies were taken from the greater and lesser curvatures in the distal and proximal antrum, and four corpus biopsies were obtained from the greater and lesser curvature of the proximal and distal corpus. Antral and corpus biopsies were separately labeled. An additional antral biopsy was taken for determination of *H. pylori* status by rapid urease test (CLOtest; Ballard, Draper, UT).

Histology. Gastric biopsy specimens were fixed in 10% buffered formalin and embedded in paraffin. The paraffin sections were stained with H&E and the modified Giemsa techniques. Histologic sections of the antrum and corpus tissue were graded for *H. pylori* density, severity of acute (polymorphonuclear cells) infiltrates, intensity of the chronic (mononuclear cells) infiltrates, glandular atrophy, and intestinal metaplasia as stipulated in the updated Sydney system (18). Intestinal metaplasia was recognized morphologically by the presence of goblet cells, absorptive cells, and cells resembling colonocytes. All variables were graded as none (0), mild (1), moderate (2), or marked (3).

Diagnosis of *H. pylori* Infection. The presence of *H. pylori* antibody in serum was tested by serology in family members who had no *H. pylori* detected in the stomach by rapid urease test and histology. Antibody against *H. pylori* was detected by Signify *H. pylori* test (Applied Biotech, San Diego, CA), which has been validated in our population (19). *H. pylori* infection was diagnosed when one of the following was present: (*a*) a positive rapid urease test, (*b*) *H. pylori* identified by histologic examination, or (*c*) the presence of *H. pylori* antibody in serum.

Statistical Analysis. Statistical analysis was done by SPSS software (version 11.5, SPSS, Inc., Chicago, IL). Possible covariables associated with the presence of intestinal metaplasia in gastric cancer relatives were analyzed. We compared the subjects' age, sex (male versus female), relationship with family members who had gastric cancer (offspring versus sibling), onset age of stomach cancer in family member (≤45 versus >45 years), number of siblings in the family, birth order (youngest versus others), smoking habits (smokers versus nonsmokers/ex-smokers), use of alcohol (drinkers versus nondrinkers), *H. pylori* infection, childhood living environments (urban versus village), and childhood drinking water supply (in-house tap versus communal tap/well). Factors with a trend of significance ($P < 0.10$) were included in the forward stepwise logistic regression model to identify for independent factors associated with presence of intestinal metaplasia in family relatives. The odds ratio (OR) with 95% confidence interval (95% CI) was presented. χ^2 for trend was used to compare the frequency of intestinal metaplasia among different age groups and sibling size. Mann-Whitney *U* test was used in the comparison of severity of inflammation scores. All *P* values were two-sided and statistical significance was taken at $P < 0.05$.

Results

Baseline Characteristics. Two hundred and seventy first-degree relatives (129 siblings and 141 offspring) of 91 gastric cancer patients were recruited in this study. All of them had one family member affected by stomach cancer only. The overall response rate of the gastric cancer relatives was 58.2%. The median age of these cancer relatives was 42 years (range 18-66) and 47% were male. In total, 161 (59.6%) family relatives were infected with *H. pylori*. During screening endoscopy, gastric ulcer was found in five (1.9%) subjects and six (2.2%) were found to have duodenal ulcer. Two relatives were found to have malignant gastric tumors on screening endoscopy: one being mucosa-associated lymphoid tissue lymphoma and the other was adenocarcinoma of stomach. Both tumors were early stage I disease.

Intestinal Metaplasia in Gastric Cancer Relatives. Eighty-one (30%) cancer relatives had histologically confirmed intestinal metaplasia in the antrum and/or corpus. Subjects with gastric intestinal metaplasia were significantly older than those without metaplasia (mean age 45.8 ± 7.9 versus 39.9 ± 8.8, $P < 0.001$). The other baseline characteristics of subjects with confirmed gastric intestinal metaplasia were listed in Table 1. In summary, male gender and history of alcohol use were significantly associated with the presence of intestinal metaplasia in these family relatives. Moreover, a history of gastric cancer in the siblings was associated with a higher risk

Table 1. Univariate analysis of baseline characteristics associated with the presence of intestinal metaplasia in gastric cancer relatives

	IM positive (n = 81)	IM negative (n = 189)	P	OR (95% CI)
Mean age	45.8 (7.9)	39.9 (8.8)	<0.001	
Male	47 (58.0%)	80 (42.3%)	0.018	1.88 (1.11-3.19)
Female	34 (42.0%)	109 (57.7%)		1.0
Family members affected				
Siblings	51 (63.0%)	78 (41.3%)	0.001	2.42 (1.42-4.32)
Parents	30 (37.0%)	111 (58.7%)		1.0
Age of family member diagnosed to have stomach cancer (y)				
≤45	23 (28.4%)	46 (24.3%)	0.48	0.81 (0.45-1.46)
>45	58 (71.6%)	143 (75.7%)		1.0
Median no. siblings	6 (1-11)	5 (1-12)	0.035	
Birth order				
Youngest	10 (12.3%)	46 (24.3%)	0.045	0.45 (0.22-0.96)
Childhood water supply				
In-house tap	38 (49%)	126 (70%)	0.002	2.4 (1.38-4.15)
Communal tap/well	39 (51%)	54 (30%)		1.0
Childhood living area				
City	51 (66%)	144 (80%)	0.018	1.0
Village	26 (34%)	35 (20%)		2.04 (1.12-3.71)
Smokers	17 (21.0%)	36 (19.0%)	0.71	1.13 (0.59-2.16)
Drinkers	34 (42.0%)	55 (29.1%)	0.039	1.76 (1.03-3.03)

Abbreviation: IM, intestinal metaplasia.

of gastric intestinal metaplasia than a parental history of gastric cancer ($P = 0.001$).

Infection with *H. pylori* significantly increased the risk of gastric intestinal metaplasia in gastric cancer relatives. *H. pylori* infection, as defined by positive test result in one of the three diagnostic tests, was associated with an OR of 5.4 (95% CI, 2.8-10.43). The risk of intestinal metaplasia associated with different *H. pylori* diagnostic tests are shown in Table 2.

Patients with intestinal metaplasia tended to have more siblings than those without metaplasia (median 6 versus 5, $P = 0.035$). As shown in Fig. 1, there was a nonsignificant trend toward progressive increase in the prevalence of intestinal metaplasia with more siblings ($P = 0.055$). On the other hand, the birth order of the cancer relatives had a borderline association with the presence of intestinal metaplasia. Subjects who were the youngest child in the family had a lower risk of intestinal metaplasia than those with other birth order (12.3% versus 24.3%, $P = 0.045$). Furthermore, childhood living environment was associated with the presence of intestinal metaplasia. Individuals who lived in rural area (42.6% versus 26.2% in urban area, $P = 0.018$) and those who did not have in-house water supply in childhood (41.9% versus 23.2%, $P = 0.002$) had a higher risk of gastric intestinal metaplasia.

When compared with subjects without intestinal metaplasia, those who had gastric intestinal metaplasia had more severe acute and chronic inflammation in the antrum as well as in the corpus ($P < 0.003$, Table 3). Whereas most study subjects had minimal to mild acute inflammation (score 0-1) in the corpus, there was considerable overlap in the median and range of the inflammatory score of relatives with or without intestinal metaplasia. The mean acute inflammatory score in the corpus of subjects with and without intestinal metaplasia was 0.77 and 0.44, respectively. Specifically, 72.5% of relatives without intestinal metaplasia and 54.3% of relatives with intestinal metaplasia had no acute inflammatory infiltrates in the stomach.

Next, we examined the potential association between the patterns of gastritis and the presence of intestinal metaplasia. Although antrum-predominant gastritis was more frequently seen in relatives with intestinal metaplasia (46% versus 36.5%), the difference did not reach statistical significance ($P = 0.28$).

Multiple Logistic Regression. Factors that were entered into the multivariate stepwise logistic regression included male sex, age (per year increase), birth order (youngest), sibling size, *H. pylori* infection status, relationship with gastric cancer relatives, childhood water supply, childhood living area, and alcohol use. After multiple logistic regression, four factors were found to be independently associated with the presence of intestinal metaplasia in the stomach: *H. pylori* infection, male gender, age, and a history of gastric cancer in siblings (Table 4). Among these four factors, *H. pylori* infection was associated with the highest adjusted OR of 3.23 (95% CI, 1.59-6.56) and was the only modifiable risk factor. Age was also found to be a significant risk factor for developing intestinal metaplasia. For every single year increase in age, the risk of having intestinal metaplasia was ~1.1-fold higher ($P = 0.001$). Alternatively, the risk of intestinal metaplasia increases by 1.9-fold for every 10-year increase in age. Moreover, male subjects and a history of gastric cancer in siblings were both associated with ~2-fold increase in risk of harboring intestinal metaplasia in the stomach of cancer relatives.

Subgroup analysis further showed that the age-dependent increase in the prevalence of intestinal metaplasia was more marked in *H. pylori*–infected individuals ($P = 0.0003$) than in *H. pylori*–negative individuals ($P = 0.28$; Fig. 2).

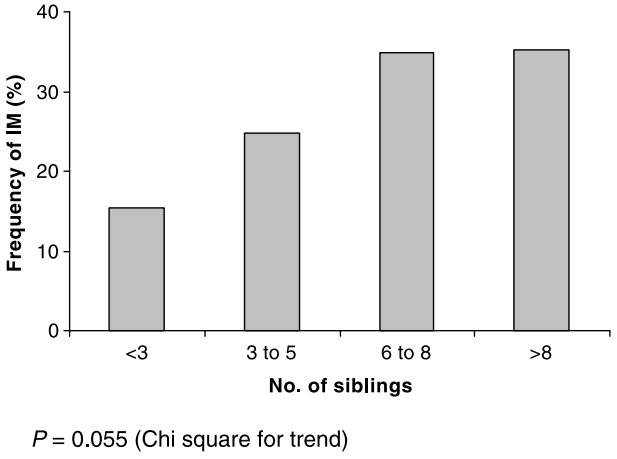

Figure 1. Association between the prevalence of gastric intestinal metaplasia (*IM*) and number of siblings in gastric cancer relatives.

Discussion

Whereas first-degree relatives of gastric cancer patients have a higher prevalence of premalignant gastric lesions (16), we determined the risk factors associated with the presence of gastric intestinal metaplasia in this group of high-risk individuals. These data will shed new lights onto various demographic and environmental factors that are associated with this apparent clustering of gastric cancer and premalignant gastric lesions in cancer relatives.

In this study, we found that *H. pylori* infection played an instrumental role in determining the risk of intestinal metaplasia among gastric cancer relatives. Individuals infected

Table 2. Risk of intestinal metaplasia based on different methods for diagnosis of *H. pylori* infection

Diagnostic test*	IM positive ($n = 81$)	IM negative ($n = 189$)	OR (95% CI)	P
Rapid urease test positive	56 (69.1%)	73 (38.6%)	3.53 (2.03-6.15)	<0.0001
Histology positive	57 (70.4%)	80 (42.3%)	3.21 (1.84-5.6)	<0.0001
Combination†	68 (84.0%)	93 (49.2%)	5.4 (2.80-10.43)	<0.001

*Because *H. pylori* serology test was only done in subjects with negative results in rapid urease test and histology, OR cannot be computed of this cohort.
†*H. pylori* infection was diagnosed if rapid urease test, histology, or serology was positive.

Table 3. Association between severity of gastric inflammation and presence of gastric intestinal metaplasia

	Histology scores	IM positive	IM negative	P*
Antrum				
AI	Median (range)	2 (0-3)	0 (0-3)	<0.001
	Mean	1.52	0.80	
	Interquartile range	0-2.5	0-2	
CI	Median (range)	2 (0-3)	1 (0-3)	<0.001
	Mean	1.96	1.25	
	Interquartile range	1-3	0-2	
Corpus				
AI	Median (range)	0 (0-3)	0 (0-3)	0.003
	Mean	0.77	0.44	
	Interquartile range	0-1	0-1	
CI	Median (range)	1 (0-3)	1 (0-3)	0.002
	Mean	1.21	0.87	
	Interquartile range	1-2	0-1	

Abbreviations: AI, acute inflammation; CI, chronic inflammation.
*Mann-Whitney *U* test.

with *H. pylori* had 3-fold increase in risk of intestinal metaplasia. We further showed that age is an important factor governing the development of intestinal metaplasia in the stomach. Interestingly, the age-dependent increase in prevalence of intestinal metaplasia was more marked in *H. pylori*–infected individuals but not in noninfected individuals (Fig. 2). These findings further support the multistep gastric carcinogenesis model (10), which takes decades to progress from chronic gastritis to intestinal metaplasia in *H. pylori*–infected subjects. Although the role of *H. pylori* eradication on chemoprevention of gastric cancer remains controversial (13-15), there is data suggesting that early eradication of *H. pylori* before the development of gastric intestinal metaplasia may prevent cancer development (20). Moreover, eradication of *H. pylori* in stomach cancer relatives is strongly recommended by leading authority (21). It may therefore be interesting to determine the role of ''test and treat'' of *H. pylori* in gastric cancer relatives in a prospective manner.

Similar to gastric cancer incidence (1), we found that men had a higher risk of developing premalignant gastric lesions when compared with women. This male predominance of gastric premalignant lesions was also noted in individuals with no family history of gastric cancer in our previous studies (14, 15).

In contrast to previous reports that typically compared the difference between stomach cancer relatives and control (2-9, 16, 22), we focused on gastric cancer relatives alone and compared the difference between those with and without gastric intestinal metaplasia. Because family members are generally considered to be at higher risk of harboring premalignant gastric lesions, it may account for the lower OR reported in this study than previous studies that used general population as controls (16, 22).

Another interesting observation of our study was that a history of gastric cancer in the siblings was an independent risk factor for intestinal metaplasia even after adjustment for possible confounding effects, particularly age. Individuals with a history of gastric cancer in the siblings had ~2-fold increase in risk of intestinal metaplasia than those with a parental history of gastric cancer. In keeping with this, Zanghieri et al. (2) showed that the increase in risk of gastric cancer among family relatives was limited to siblings but not to parents. Although the exact reason for this clustering pattern remains elusive, we believed that environmental factors, particularly *H. pylori* infection and childhood living conditions, play an important role. Chang et al. (22) reported that the prevalence of *H. pylori* infection was substantially higher in individuals with a history of gastric cancer in the siblings (adjusted OR, 5.3) when compared with those with parental history of gastric cancer (adjusted OR, 1.7) In our study, we noted that individuals living in rural areas and without in-house tap water supply in childhood had a higher risk of developing intestinal metaplasia. Moreover, the prevalence of intestinal metaplasia in the stomach tended to increase with the number of siblings in the family. All these adverse childhood conditions are recognized risk factors for contracting *H. pylori* infection (23, 24), which may indirectly explain the risk of developing gastric intestinal metaplasia.

Table 4. Multiple logistic regression analysis of factors associated with presence of gastric intestinal metaplasia in gastric cancer relatives

Factors	*P*	Adjusted OR (95% CI)
H. pylori infection	0.001	3.23 (1.59-6.56)
Male sex	0.017	2.09 (1.14-3.84)
Gastric cancer in siblings	0.039	1.91 (1.03-3.55)
Age		
Per year increase	0.001	1.07 (1.03-1.12)
Per 10-year increase	0.001	1.94 (1.29-2.90)

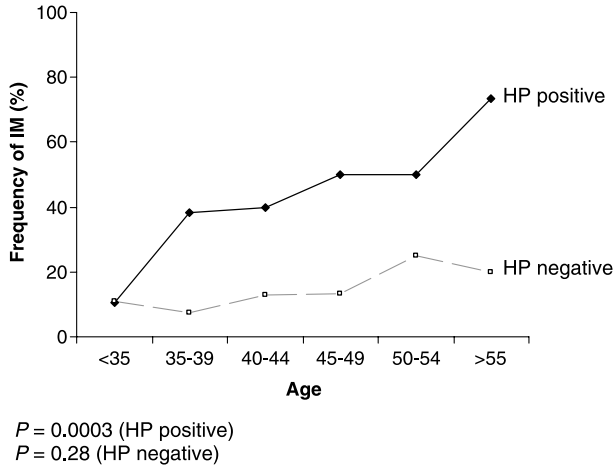

Figure 2. Age-dependent changes in prevalence of gastric intestinal metaplasia in *H. pylori* (*HP*)–infected family relatives.

This study mainly focused on Chinese who are at much higher risk of developing gastric cancer than subjects from Western countries. In contrast to most Western studies, the role of harboring *cag*A+ *H. pylori* strains remains elusive in Chinese population. Past studies showed that virtually all Chinese strains are *cag*A+ and it is therefore not feasible to have further subgroup analysis (25, 26). Moreover, most of our patients are suffering from noncardia cancer, which has a much stronger association with *H. pylori* infection.

The major limitation of this study is the cross-sectional design. In particular, the age effect may be confounded by other potential risk factors for intestinal metaplasia present at that time. Our result should ideally be confirmed by future prospective studies. Another limitation of this kind of study is the nonparticipation rate by asymptomatic cancer relatives, which may result in sampling or selection bias. Whereas endoscopy is an uncomfortable procedure, 100% participation by cancer relatives is an unrealistic goal to achieve. However, this drawback may be partly overcome by recruiting a reasonable sample of cancer relatives as in our study.

In conclusion, we have identified a number of risk factors associated with the development of premalignant gastric lesion in gastric cancer relatives. Our data showed that *H. pylori* infection, old age, male subjects, and a history of gastric cancer in the siblings are independent risk factors for developing gastric intestinal metaplasia. Whereas screening and surveillance of subjects with premalignant gastric lesions has been shown to detect tumors at an early stage (27), screening endoscopy may be more appropriate if directed to this subgroup of high-risk individuals. Future studies should examine the role of ''test and treat'' of *H. pylori* infection in preventing the development of premalignant gastric lesions in gastric cancer relatives.

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