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Risk Factors of Intestinal Metaplasia in Northwest of China

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Abstract

The aim of this study was to find out the risk factors of gastric intestinal metaplasia (IM) in northwest of China. A retrospective case-control study was conducted with a well-designed questionnaire, including basic information and related factors. Totally 2157 subjects with benign upper gastrointestinal disorders from Xijing hospital and the second affiliated hospital of Xi'an Jiaotong University were enrolled in this study, among which 332 cases were patients with IM and another 1825 patients without IM served as controls. The IM was diagnosed by gastroscopy and/or gastric mucosal pathology. *Helicobacter pylori (H. pylori)* infection was measured by ^{13}C- or ^{14}C-urea breath test or by rapid urease test. The multivariate analysis showed that the risk factors of IM were age ≧ 60yr (OR, 2.27; 95% CI, 1.70 to 3.03; P < 0.001), *H. pylori* infection (OR, 2.67; 95% CI, 2.22 to 3.21; P < 0.001), smoking (OR, 2.20; 95% CI, 1.54 to 3.15; P < 0.001), family history of gastric cancer (OR, 2.22; 95% CI, 1.48 to 3.33; P < 0.001), high salt diet (OR, 1.58; 95% CI, 1.18 to 2.13; P = 0.002) and spicy food (OR, 1.46; 95% CI, 1.08 to 1.96; P = 0.013). These results indicate that the risk factors of IM in northwest of China are consistent to well-known risk factors for gastric cancer, and patients with age ≧ 60 yr, *H. pylori* infection, smoking, family history of gastric cancer, high salt diet and spicy food should be followed-up and screened for IM and gastric cancer.

Keywords

Intestinal metaplasia, Precancerous lesion, Risk factors, Gastric cancer, Helicobacter pylori

Introduction

Gastric cancer (GC) is the 4th in cancer incidence and the second in most common cause of cancer-related deaths worldwide [1]. A large number of clinical investigations showed that the 5-year survival rate of the patients with advanced gastric cancer is less than 20%, whereas for the early gastric cancer, the 5-year survival rate is as high as 90% [2]. Correa model suggests that gastric cancer usually develops from chronic superficial gastritis, chronic atrophic gastritis, intestinal metaplasia (IM), a typical hyperplasia and eventually to cancer [3]. Among these conditions, gastric IM and atypical hyperplasia are precancerous lesions of GC. In general, there should be about 10 to 20 years for gastric IM evolve into gastric cancer. However, the time for atypical hyperplasia is about 3 to 5 years. Therefore, gastric IM should be focused on to control and prevent the procedure of gastric cancer. As reported, the appearance of IM will increase the incidence of GC by 10.9-fold [4]. It's vital to monitor the onset of IM and to take some intervening measures especially the person with high risk factors in order to decrease the incidence of GC.

Gastric IM means that the gastric normal mucosa epithelial cells are replaced by the intestinal morphology cells which consist of paneth cells, absorptive cells and goblet cells [5]. There are two types of IM, small intestinal type (complete IM) and colonic type (incomplete IM) of IM. Small intestinal type is more related to inflammatory disease and colonic type of IM is more common in the adjacent tissues of GC [6,7].

The prevalence of IM varies according to the incidence of GC. China is a country with high incidence of GC. There were a variety of risk factors leading to the appearance of IM according to the current reports. Among them, *Helicobacter pylori* (*H. pylori*) infection was reported to play the most important role in the procedure [8-10]. Age, smoking, high salt diet, bile reflux, obesity, relatives of GC and some other risk factors were reported to accelerate the process of IM.

According to the former study, there were few large-scale clinical reports analyzing the risk factors about IM in China. To this point, the present study aimed to find out the risk factors of gastric IM in northwest of China by a case-control study.

Statement of Methods

Study population

This was a retrospective case-control study. A total of 2157

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Table 1: Baseline characteristics of the 2157 subjects.

Variable	Value
Age, yr	49.2 ± 11.7
≦ 39	430 (19.9%)
40-59	1300 (60.3%)
≧ 60	427 (19.8%)
Gender, male	1037 (48.1%)
Body mass index, kg/m^2	22.5 ± 3.3
Smoking	
Never	1645 (76.3%)
Current	425 (19.7%)
Previous	87 (4.0%)
Alcohol	
Never	1912 (88.6%)
Current	194 (9.0%)
Previous	51 (2.4%)
H. pylori infection	828/1571 (52.7%)
Family history of GC	147 (6.8%)
Bile reflux	156 (7.2%)
Diarrhea	273 (12.7%)
Constipation	415 (19.2%)
Tea intake, ≧ 6 cups (250 ml per cup) / wk	264 (12.2%)
High salt diet, ≧ 15 g common salt / d	501 (23.2%)
Spicy food, ≧ 4 times / wk	567 (26.3%)
Vitamin C, ≧ 3 m	28 (1.3%)
The consumption of dairy products, ≧ 100 g/d	536 (24.8%)
The consumption of fruits, ≧ 300 g/d	740 (34.3%)
The consumption of vegetables, ≧ 200 g/d	1800 (83.4%)
NSAIDs use, ≧ 3 m	48 (2.2%)
Income level, ≧ 3500 RMB	911 (42.2%)
Education, above college	448 (20.8%)

Continuous variables are expressed as mean ± SD, whereas categorical data are expressed as n (%).

Table 2: The detection rate of IM.

	Percentage (%)
The number of IM (n = 332)	332/2157 (15.4%)
Mild	256/332 (77.15%)
Moderate	58/332 (17.5%)
Sever	18/332 (5.4%)

subjects who came to the gastroenterology clinic in Xijing hospital and the second affiliated hospital of Xi'an Jiaotong University in China with the results of gastroscopy and/or gastric mucosal pathology from August 2014 to August 2015 were enrolled in the present study. All subjects who had a history of gastrointestinal surgery, had systemic diseases requiring long-term medication or diagnosed with high-grade intraepithelial neoplasia or cancer were excluded from the study. We obtained the informed consent from all participating individuals and all information was protected securely.

Questionnaire

All of the 2157 subjects underwent a clinical interview which was based on a well-designed questionnaire by consulting the epidemiology and statistics specialists. All the interviewers were well-trained before the start of the study. In this questionnaire, the questions included demographic data, the upper gastrointestinal symptoms, such as acid reflux, heartburn, hiccup, eructation, abdominal distention and pain, poor appetite, nausea, vomiting, dyspepsia, the condition of constipation and diarrhea, smoking condition, alcohol consumption, the intake of tea and coffee, salt and spicy food intake, the consumption of fruits, vegetables, vitamin C and dairy products, the use of non-steroidal anti-inflammatory drugs (NSAIDs), *H. pylori* infection, family history of gastric cancer, the income level and education condition.

Endoscopic and histological results

All the endoscopic results that were benign gastric disorders, such as chronic superficial gastritis, chronic atrophic gastritis, and gastric ulcer with or without IM were enrolled in this study. They were divided into case and control groups depending on that if existed IM. The diagnosis of these diseases was confirmed with gastro-duodenal endoscopy and/or biopsy pathology. *H. pylori* infection was measured by ^{13}C- or ^{14}C-urea breath test or by rapid urease test. Bile reflux was diagnosed with gastro-duodenal endoscopy.

Statistical analysis

All statistical date were showed by the percentage rate or mean ± standard deviation (SD). The Student's t-test were used for continuous variables, categorical data were analyzed by chi-squared test or Fisher's exact test. In order to analyze the risk factors, multivariate logistic regression analysis were used in this study presented by the odds ratio (OR) and 95% confidence interval (CI). P-values < 0.05 was regarded as a statistically significant difference. All the P-values in this study were two-sided. The statistical data were analyzed by the Statistical Package for Social Science software suite (version 19.0; SPSS, Ink, Chicago, IL, USA).

Summary of Results

Baseline characteristics of subjects

A total of 2157 subjects were enrolled in this study. The age of all the subjects ranged from 16 to 85 years old with the peak of 40 to 59 years old. Among them, the male and female subjects were half to half. There were 1571 subjects presented *H. pylori* infection data and the positive ratio was 52.7%. As shown in table 1, the factors surveyed in the present study included body mass index (BMI), smoking, alcohol consumption, family history of gastric cancer, bile reflex, diarrhea, constipation, dietary factors, NSAIDs use condition, income level and education level.

Detection rate of IM

In this study, 332 cases were found with IM and classified as case group whereas another 1825 subjects without IM were defined as control group. The majority of the cases were with mild IM, and only 5.4% of cases were severe IM (Table 2).

The relevant risk factors for IM by univariate and multivariate analysis

In the univariate analysis, we found that age ≧ 60 yr, male gender, *H. pylori* infection, smoking, alcohol consumption, high salt diet, spicy food, tea intake, family history of gastric cancer, consumption of vegetables were all proved to be relevant factors for IM (Table 3).

All the ten relevant factors proved by univariate analysis were pooled to multivariate analysis. As shown in table 4, there were six factors significantly associated with IM, including age ≧ 60 yr, *H. pylori* infection, smoking, family history of GC, high salt diet and spicy food. Another four factors including gender, alcohol consumption, tea intake, consumption of vegetables, were proved not independent risk factors of IM.

Discussion

The GC is still a major cause of cancer related death worldwide [11]. Gastric IM is an important precancerous lesion for GC. The presence of IM will increase the incidence of GC significantly. Therefore, it's extremely necessary to clarify the risk factors for IM so that appropriate intervention could be taken to decrease the incidence of IM and GC. A variety of risk factors, such as *H. pylori* infection, gender, age, smoking, alcohol, the family history of GC, high salt intake, spicy food, bile reflux, low income level and poor education condition have been reported to increase the risk of IM [12-15]. In our study, we found that age ≧ 60 yr, *H. pylori* infection, smoking, high salt diet, spicy food, family history of GC were risk factors, which agrees with the former reports.

According to the previous studies, *H. pylori* infection was a major risk factor for both IM and GC. After eliminating the *H. pylori*, the prevalence rate of IM decreased and the state of the patients was

Table 3: Univariate analysis of the risk factors for IM.

Variable	IM (+) (n = 332)	IM (-) (n = 1825)	P-value
Age ≧ 60 yr	99/332 (29.8%)	328/1825 (18.0%)	p < 0.001
BMI ≧ 28	21/332 (23.8%)	102/1825 (21.5%)	0.662
Gender, male	194/332 (58.45)	843/1825 (46.2%)	p < 0.001
H. pylori			p < 0.001
(+)	221/300 (73.7%)	607/1271 (47.8%)	
(-)	79/300 (26.3%)	664/1271 (52.2%)	
Smoking	131/332 (39.5%)	381/1825 (20.9%)	p < 0.001
Alcohol	68/332 (20.5%)	177/1825 (9.7%)	p < 0.001
Family history of GC	47/332 (14.2%)	100/1825 (5.5%)	p < 0.001
Bile reflux	32/332 (9.6%)	124/1825 (6.8%)	0.083
Diarrhea	47/332 (14.2%)	226/1825 (12.4%)	0.419
Constipation	74/332 (22.3%)	341/1825 (18.7%)	0.130
Tea intake	66/332 (19.9%)	198/1825 (10.8%)	p < 0.001
High salt diet	115/332 (34.6%)	386/1825 (21.2%)	p < 0.001
Spicy food	128/332 (38.6%)	439/1825 (24.1%)	p < 0.001
Vitamin C	6/332 (1.8%)	22/1825 (1.2%)	0.547
Consumption of dairy products	89/332 (26.8%)	447/1825 (24.5%)	0.479
Consumption of fruits	114/332 (34.3%)	626/1825 (34.3%)	0.873
Consumption of vegetables	258/332 (77.7%)	1542/1825 (84.5%)	0.008
NSAIDs use	9/332 (2.7%)	39/1825 (2.1%)	0.542
Income level ≧ 3500 RMB	153/332 (46.15%)	758/1825 (41.5%)	0.192
Education above college	77/332 (23.2%)	371/1825 (20.3%)	0.514

Data are presented as number (%).

Table 4: Multivariate analysis of the risk factors for IM.

Variable	B	SE	P-value	Exp(β)	95% CI	
					Lower	Upper
Age ≧ 60 yr	0.820	0.148	< 0.001	2.270	1.699	3.034
Gender, male	-0.018	0.173	0.919	0.983	0.700	1.380
H. pylori infection	0.982	0.095	< 0.001	2.670	2.218	3.214
Smoking	0.789	0.183	< 0.001	2.201	1.536	3.152
Alcohol	0.364	0.195	0.062	1.438	0.982	2.107
Family history of GC	0.799	0.206	< 0.001	2.223	1.484	3.329
Tea intake	0.196	0.182	0.281	1.216	0.852	1.737
High salt diet	0.459	0.152	0.002	1.582	1.176	2.130
Spicy food	0.376	0.151	0.013	1.456	1.084	1.957
Consumption of vegetables	-0.198	0.163	0.224	0.820	0.595	1.129

B: Estimate; SE: Standard Error; Exp(β): Odds Ratio; CI: Confidence Interval.

improved [9]. The present study showed that *H. pylori* infection is still the most important and independent risk factor for IM. It is generally believed that *H. pylori* infection is an important cause of GC, and eradicating the *H. pylori* before the appearance of IM and atypical hyperplasia can reduce the incidence of GC by 30-40% [16]. Recently a study with 15-years of follow-up in a high incidence of GC area, Shandong LinQu, showed that the eradication of *H. pylori* can also reduce the incidence of GC when IM existed already [17]. Therefore, *H. pylori* infection is closely related to gastric IM and GC. However, it should be noted that not all the subjects enrolled in the present study presented *H. pylori* infection data. A well-designed prospective study is needed to clarify the influence of *H. pylori* infection on gastric IM.

Age is also an important risk factor [18]. The research from Italy and Colombia showed that the detection rate of IM in elder patients increased significantly compared with younger ones. South Korea's recent study also found that gastric IM detection rate was markedly increased with age and had a good linear relationship [19]. This study also showed that the detection rate of gastric IM was as high as 70% above 60 yrs. We also found that, the incidence rate was higher and degree of IM was severer in patients above 60 yrs compared with the patients under 40 yrs. This was consistent with the peaking age of gastric cancer incidence, which suggests strong relation of IM with GC.

It's well-known that smoking is closely related to various cancers. However, there were lots of reports having opposite viewpoints about the influence of smoking on IM [20]. In our study, we found current smokers and former smokers were more likely to IM compared with the cases who never smoked. Smoking was exactly a risk factor for IM in Chinese people. We'd better encourage the patients to quit smoking as possible.

In our study, we got a conclusion that high-salt diet and spicy food had a clear effect on the incidence of IM. It is speculated that high-salt diet and spicy food possibly decrease the gastric mucus viscosity and then led to the destruction of the protective mucous barrier [21]. If the subjects were infected with *H. pylori* meanwhile, we could see that they were more inclined to appear IM (OR, 3.39; P < 0.001). There must be some synergistic effects between *H. pylori* and high-salt diet and spicy food. As conformed that high salt diet could reduce the number of surface mucous cell mucin to accelerate the colonization of *H. pylori* and then stimulate and afford the suitable environment for the development of *H. pylori* [21]. These data indicate that it's extraordinary important to reduce the intake of high-salt and spicy food for the prevention of IM.

The history of gastric cancer was also an important risk factor for the development of IM [22]. It's reported that about 10% of GC has the phenomenon of familial aggregation, this may be related to the same life style, living environments, eating habits and their similar genetic backgrounds [23]. As a precancerous lesion, gastric IM also has certain familial aggregation phenomenon. Our research also showed that family history of GC was an independent risk factor for gastric IM. The first-degree relatives of patients with GC should be educated and encourage receiving gastroscopy examination regularly.

There were four factors showing significant differences between case group and control group in univariate analysis but exhibiting no association with IM in multivariate analysis, which included gender,

alcohol consumption, tea intake, consumption of vegetables. Among them, tea especially green tea has been proven by many studies to inhibit gastrointestinal cancer development with its antioxidant activity. It is reasonable that green tea may also have protective effects on the development of IM. However, there were only 66 and 198 subjects taking tea in the case and control groups respectively. The protective effects of tea maybe concealed due to these small samples. A larger scale survey is encouraged to further illustrate the exact role of tea in gastric IM.

There still were some limitations in our study. Firstly, our cases mainly came from Xijing hospital of the Fourth Military Medical University and the Second Affiliated Hospital of Xi'an Jiaotong University clinics. There may be some differences on the diagnosis of IM between different doctors, which may affect the observation group and some mild IM would be missed and divided into the control group. Secondly, the cases in our study mainly came from northwest of China, which cannot represent the conditions all over the country. At last, the recalling and responding bias about the questionnaire could not be controlled completely.

As a conclusion, the risk factors of IM in northwest of China were age ≧ 60 yr, *H. pylori* infection, smoking, high salt diet, spicy food and family history of GC. The elder person with a family history of GC should have a more frequent endoscopy check-up (take biopsy if necessary). For the patients with *H. pylori* infection, we would suggest eradicative treatment, having a healthy life style, avoiding smoking and high salt diet and spicy food.

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