ORIGINAL RESEARCH

Risk factors for gastric intraepithelial neoplasia in Chinese adults: a case–control study

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Background: Gastric carcinoma (GC) is the third most frequent malignancy and the second most common cancer-related cause of death cause worldwide. Gastric intraepithelial neoplasia (GIN) is a well-documented precancerous lesion of GC. In this case–control study, we comprehensively explored the clinical and pathological characteristics of GIN, with the aim to identify its potential risk factors.

Patients and methods: A total of 630 consecutive patients who underwent endoscopic submucosal dissection or mucosal resection for GIN were initially included. The detailed characteristics of all eligible patients and well-matched healthy controls were recorded and analyzed. Both univariate and multivariate logistic regression analyses were performed and presented with odds ratio (OR) and 95% confidential interval (CI), with additional subgroup analyses based on lesion location.

Results: A total of 485 GIN-eligible patients were selected, among which 156 had proximal GIN. After follow-up, 434 patients with GIN and 310 age- and gender-matched healthy controls were included in the comparative analyses. Family cancer history (FCH); alcohol abuse; tobacco abuse; intake of high sodium, preserved food, spicy food, and less fruit; *Helicobacter pylori* (Hp) infection; and atrophic gastritis with intestinal metaplasia were more frequent in GIN patients. Thus, FCH (OR =3.485, 95% CI: 2.031–5.981), high sodium intake (OR =2.830, 95% CI: 1.645–4.868), less fruit intake (OR =4.082, 95% CI: 2.515–6.625), Hp infection (OR =2.307, 95% CI: 1.417–3.755), and atrophic gastritis with intestinal metaplasia (OR =15.070, 95% CI: 8.999–25.237) were independent risk factors for GIN. Further subgroup analyses demonstrated that the specific independent risk factor for proximal GIN was age (OR =2.001, 95% CI: 1.003–3.994), whereas that for distal GIN was intake of high sodium (OR =3.467, 95% CI: 1.896–6.338).

Conclusion: This study reported a comprehensive overview of the clinical and pathological characteristics of GIN. FCH, high sodium intake, less fruit intake, Hp infection, and atrophic gastritis were identified as the independent risk factors for GIN.

Keywords: gastric intraepithelial neoplasia, risk factor, case–control study, subgroup analysis

Introduction

Gastric carcinoma (GC) is the third most common malignancy worldwide with approximately 1.3 million newly diagnosed cases.[1] In People's Republic of China, GC ranks as the second most frequently occurring cancer and cause of cancer deaths; approximately 679,100 new cases and 498,000 GC-related deaths were projected to occur in 2015.[2] The prognosis of GC differs significantly in accordance with various stages; the 5-year overall survival rate of early GC is over 90%, while that of advanced

GC is about 15%.[3] Early diagnosis and treatment of GC could contribute to the prolonged survival of GC patients.[4]

Gastric intraepithelial neoplasia (GIN) is well accepted as a precancerous lesion of GC, which can be divided into 2 categories according to lesion location: proximal and distal intraepithelial neoplasia (PGIN and DGIN, respectively).[5] The annual incidence of GC is 6% for high-grade GIN patients within 5 years after diagnosis.[6] To date, numerous efforts have been devoted to identify the clinical and epidemiological features of GC;[7,8] however, GIN remains poorly understood. Furthermore, previous studies demonstrated that proximal and distal GC (PGC and DGC) are 2 distinct entities with different epidemiologic, clinicopathologic, and molecular biological features.[9–11] Hence, it is of vital importance to explore the potential variety between risk factors for PGIN and DGIN.

In the current study, we retrospectively enrolled 485 GIN patients to provide a comprehensive overview of the clinical and pathological features of GIN. Furthermore, 310 age- and gender-matched healthy volunteers were recruited for comparison to identify the potential risk factors for GIN.

Patients and methods
Patient selection
From January 2007 to December 2014, 630 consecutive patients who underwent endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) for GIN at Nanjing Drum Tower Hospital were initially included in the current study. The inclusion criteria were set as follows: 1) age ≥18 years and 2) pathologically diagnosed with GIN after ESD/EMR by 2 independent experienced pathologists. The exclusion criteria were as follows: 1) pathologically diagnosed with GC after operation, 2) multifocal lesion which was defined as the distance between 2 lesions over 20 mm, 3) a history of GC, and 4) tumor located at distal esophagus and gastroesophageal junction. The detailed selection criteria are demonstrated in Figure 1. A total of 485 patients with GIN were finally enrolled in this study. Furthermore, 310 gender- and age-matched outpatients who underwent endoscopy and biopsy confirmed to be negative for GC or GIN were recruited as the control group. The study protocol was approved by the institutional review board of Nanjing Drum Tower Hospital, and written informed consent was obtained from all individual participants.
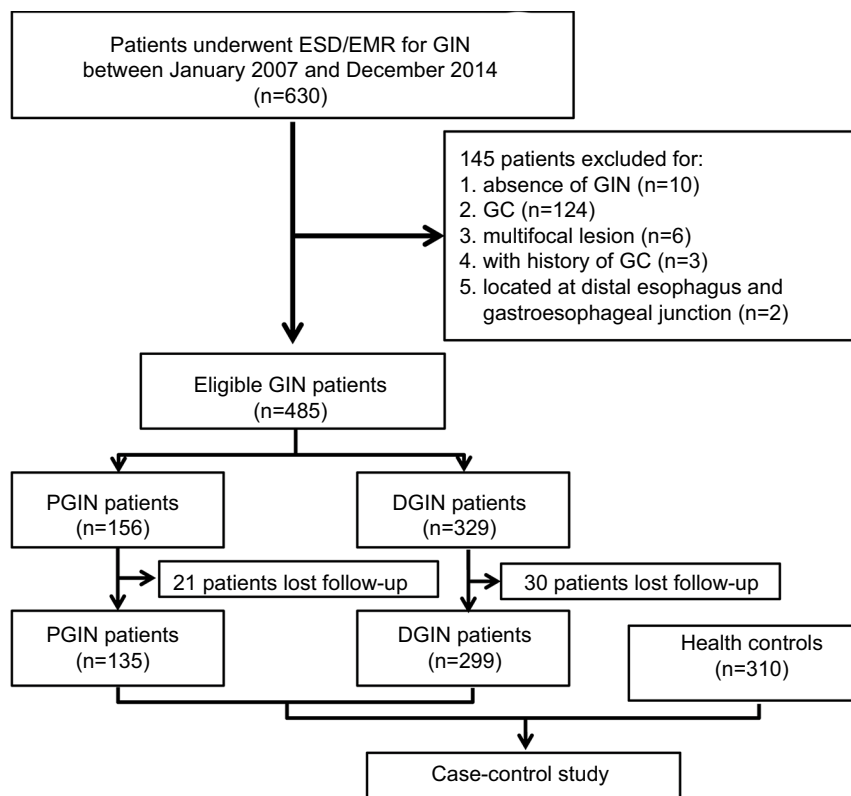
Figure 1 Study flow chart.
Notes: A total of 485 eligible GIN patients were included in this study, among which 434 patients with detailed follow-up information were compared with 310 well-matched controls.
Abbreviations: EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; GC, gastric carcinoma; GIN, gastric intraepithelial neoplasia; DGIN, distal GIN; PGIN, proximal GIN.

Study procedure

All endoscopy procedures including ESD/EMR were performed by well-trained physicians. The endoscopic morphology of superficial lesions was recoded according to the Paris classification system.[12] The representative histologic images of low- and high-grade GIN are shown in Figure 2A and B, respectively. Furthermore, the GIN lesions were categorized into 2 groups: PGIN, which was defined as a lesion located within 30 mm from the gastroesophageal junction and DGIN, which was described as a lesion located in the remaining regions. The electronic medical records were thoroughly reviewed, and clinical follow-up was performed by office visit or telephone contact. Information, including history of cancer, personal history, dietary habit, and present relevant diseases, were collected in a uniform form as was previously reported.[13] Table S1 presents the detailed items and corresponding definitions.

Statistical analysis

The continuous variables are presented as mean ± SD after the confirmation of normal distribution and were compared using Student's t-test or 1-way analysis of variance test. The categorical variables are presented as counts and percentages and compared with χ^2 statistics or Fisher's exact test when appropriate. To identify the potential risk factors, the univariate and multivariate logistic regression analyses were applied and are presented as odds ratio (OR) with the corresponding 95% confidential interval (95% CI). The statistical analyses were performed using SPSS (version 22.0; IBM Corporation, Armonk, NY, USA), and statistical significance was taken as a 2-sided P-value <0.05.

Results

Baseline clinical and pathological characteristics

A total of 485 GIN patients were enrolled in this study. Among these participants, 156 were diagnosed with PGIN (Figure 2C). The proportion of incident PGIN cases increased gradually from 13.6% in 2007–2008 to 35.3% in 2012–2014 (Figure 2D). The mean age was 62.3 years and differed between 2 groups (PGIN vs DGIN: 63.8±8.5 vs
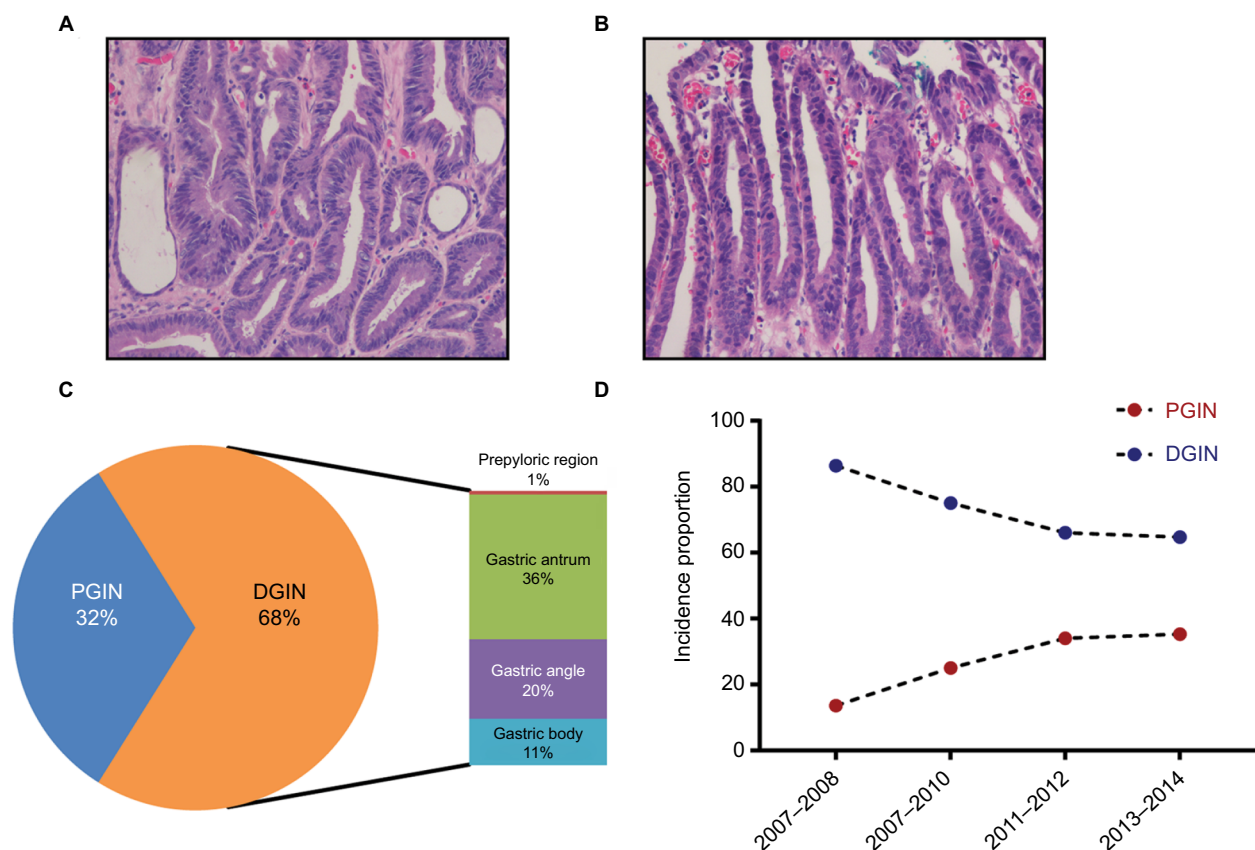
Figure 2 Overview of GIN distribution.
Notes: Representative histological images of low-grade intraepithelial neoplasia (**A**); high-grade intraepithelial neoplasia (**B**); location distribution of GIN (**C**); and proportion of 2 GIN types (**D**). (**A**, **B**) Magnification was set at ×200.
Abbreviations: GIN, gastric intraepithelial neoplasia; DGIN, distal GIN; PGIN, proximal GIN.

61.6±9.4 years, *P*=0.018; Table 1). As summarized in Table 1, significant differences were observed in the distributions of age, gender, endoscopic morphology, histologic grade, occurrence of gastritis cystica profunda, and pancreatic metaplasia between PGIN and DGIN patients. During the follow-up period, 51 (10.5%) were patients lost to follow-up, and the remaining 434 GIN patients with 310 age- and gender-matched healthy controls were included in the comparative analyses (Figure 1).

Comparison of risk factors for GIN and subgroup analyses stratified by PGIN and DGIN

Compared to the control group, family cancer history (FCH); alcohol abuse; tobacco abuse; intake of high sodium, preserved food, spicy food, less fruit; *Helicobacter pylori* (Hp) infection, and atrophic gastritis with intestinal metaplasia were more frequent in GIN patients (Table 2). Further stratification analyses revealed the similar results in both groups, except that the number of patients with PGIN aged

over 60 years was higher than that of patients with DGIN (*P*=0.001, Table 2).

Identification of risk factors for GIN

To identify potential risk factors for GIN, univariate logistic regression analyses were conducted, and it was found that FCH; alcohol abuse; tobacco abuse; intake of high sodium, preserved food, spicy food, and less fruit; Hp infection; and atrophic gastritis with intestinal metaplasia were found as potential risk factors for GIN (Table 3). The subgroup analyses showed that age (≥60 years) was a high risk for PGIN (OR =2.265, 95% CI: 1.455–3.524, *P*=0.001) than for DGIN (OR =1.348, 95% CI: 0.975–1.864, *P*=0.070).

Subsequently, multivariate logistic regression analyses were performed (Table 4). FCH, high sodium intake, less fruit intake, Hp infection, and atrophic gastritis with intestinal metaplasia were identified as independent risk factors for GIN. Further stratification analyses confirmed that FCH, less fruit intake, Hp infection, and atrophic gastritis with intestinal metaplasia were independent risk factors for both PGIN and

Table 1 Clinical and pathological characteristics of patients with GIN

Variables	GIN (n=485)	PGIN (n=156)	DGIN (n=329)	*P*-value
Age (years)				
Mean ± SD	62.3±9.2	63.8±8.5	61.6±9.4	0.018
≤40	3 (0.6%)	1 (0.6%)	2 (0.6%)	0.048
41–50	52 (10.7%)	10 (6.4%)	42 (12.8%)	
51–60	147 (30.3%)	40 (25.7%)	107(32.5%)	
61–70	188 (38.8%)	73 (46.8%)	115 (35%)	
≥71	95 (19.6%)	32 (20.5%)	63 (19.1%)	
Gender				
Male	367 (75.7%)	131 (84.0%)	236 (71.7%)	0.003
Female	118 (24.3%)	25 (16.0%)	93 (28.3%)	
Endoscopic morphology				
I	183 (37.7%)	48 (30.8%)	135 (41.0%)	0.001
IIa	81 (6.7%)	16 (10.3%)	65 (19.7%)	
IIb	72 (14.8%)	29 (18.5%)	43 (13.1%)	
IIc	122 (25.2%)	51 (32.7%)	71 (21.6%)	
III	27 (5.6%)	12 (7.7%)	15 (4.6%)	
Lesion size (cm)				
Mean ± SD	2.6±1.1	2.5±1.3	2.7±1.2	0.369
Histological grade				
Low grade	237 (48.9%)	57 (36.5%)	180 (54.7%)	<0.001
High grade	248 (51.1%)	99 (63.5%)	149 (45.3%)	
Surrounding mucosa manifestation				
Chronic gastritis	478 (98.6%)	154 (98.7%)	324 (98.5%)	0.838
Intestinal metaplasia	434 (89.5%)	134 (85.9%)	300 (91.2%)	0.076
Mucosal atrophy	431 (88.9%)	133 (85.3%)	298 (90.6%)	0.082
Hp infection	262 (54.0%)	75 (48.1%)	187 (56.8%)	0.071
Pancreatic metaplasia	3 (0.61%)	3 (1.3%)	0 (0%)	0.033
Gastritis cystica profunda	33 (6.8%)	24 (15.4%)	9 (2.7%)	<0.001

Abbreviations: GIN, gastric intraepithelial neoplasia; PGIN, proximal GIN; DGIN, distal GIN; Hp, *Helicobacter pylori*.

Table 2 Comparison of subject characteristics between groups

Variables	Control (n=310)	GIN (n=434)		PGIN (n=135)		DGIN (n=299)	
	Data	Data	*P*-value	Data	*P*-value	Data	*P*-value
Age (years)							
Mean ± SD	61.25±10.80	62.02±9.03	0.308	63.07±8.45	0.167	61.77±9.28	0.526
<60	140 (45.2%)	151 (34.8%)	0.098	37 (27.4%)	0.001	114 (38.1%)	0.070
≥60	170 (54.8%)	386 (65.2%)		98 (72.6%)		185 (61.9%)	
Gender							
Male	215 (69.4%)	325 (74.9%)	0.096	103 (76.3%)	0.136	222 (74.2%)	0.180
Female	95 (30.6%)	109 (25.1%)		32 (23.7%)		77 (25.8%)	
Hp infection							
Positive	93 (30.0%)	233 (53.7%)	<0.001	61 (45.2%)	<0.001	172 (57.5%)	0.001
Negative	216 (69.7%)	201 (46.3%)		74 (54.8%)		127 (42.5%)	
BMI							
Average ± SD	23.51±2.87	23.69±3.37	0.459	24.02±3.17	0.129	23.57±3.45	0.821
BMI <18.5	14 (4.5%)	18 (2.8%)	0.171	6 (4.5%)	0.561	12 (4.0%)	0.165
18.5≤ BMI ≤24.0	187 (60.3%)	230 (47.2%)		72 (53.3%)		158 (52.8%)	
24.0< BMI ≤28.0	97 (31.3%)	160 (36.2%)		51 (37.8%)		109 (36.5%)	
BMI >28.0	12 (3.9%)	26 (6.7%)		6 (4.4%)		20 (6.7%)	
History of cancer							
Personal	6 (1.9%)	8 (1.8%)	0.927	1 (0.7%)	0.352	7 (2.3%)	0.729
Family	55 (17.7%)	187 (43.1%)	<0.001	52 (38.5%)	<0.001	135 (45.2%)	<0.001
Personal history							
ETE	51 (16.5%)	60 (13.8%)	0.321	15 (11.1%)	0.145	45 (15.1%)	0.635
Use of NSAIDs	18 (5.8%)	28 (6.5%)	0.719	11 (8.1%)	0.358	17 (5.7%)	0.949
Tobacco abuse	115 (37.1%)	247 (56.9%)	<0.001	76 (56.3%)	<0.001	171 (57.2%)	<0.001
Alcohol abuse	114 (36.8%)	234 (53.9%)	<0.001	72 (53.3%)	<0.001	162 (54.2%)	<0.001
Dietary habit							
High sodium	132 (42.6%)	338 (77.9%)	<0.001	97 (71.9%)	<0.001	241 (80.6%)	<0.001
Preserved food	83 (26.9%)	234 (53.9%)	<0.001	67 (49.6%)	<0.001	167 (55.9%)	<0.001
Spicy food	53 (17.1%)	173 (39.9%)	<0.001	49 (36.3%)	0.010	124 (41.5%)	<0.001
Smoked food	8 (2.6%)	13 (3.0%)	0.690	3 (2.2%)	0.472	10 (3.3%)	0.888
Fried food	14 (4.5%)	38 (8.8%)	0.259	10 (7.4%)	0.671	28 (9.4%)	0.195
Hot food	74 (23.9%)	172 (39.6%)	0.106	57 (42.2%)	0.085	115 (38.5%)	0.215
Less fruit	99 (31.9%)	297 (68.4%)	<0.001	96 (71.1%)	<0.001	201 (67.2%)	<0.001
Less vegetable	45 (14.5%)	55 (12.7%)	0.467	14 (10.4%)	0.236	41 (13.7%)	0.776
Present relevant illness							
Anxiety/depression status	68 (21.9%)	108 (24.9%)	0.133	36 (26.7%)	0.455	72 (24.1%)	0.109
Hypertension	62 (20.0%)	108 (24.9%)	0.118	36 (26.7%)	0.119	72 (24.0%)	0.224
Diabetes mellitus	22 (7.1%)	43 (9.9%)	0.181	11 (8.1%)	0.697	32 (10.7%)	0.118
GERD	99 (31.9%)	120 (27.7%)	0.206	41 (30.4%)	0.215	79 (26.4%)	0.135
Hiatal hernia	3 (1.0%)	3 (0.7%)	0.678	2 (1.5%)	0.636	1 (0.3%)	0.333
Columnar-lined esophagus	2 (0.6%)	9 (2.1%)	0.111	3 (2.2%)	0.144	6 (2.0%)	0.140
Gastric intestinal metaplasia and atrophy	112 (36.1%)	375 (86.4%)	<0.001	122 (90.4%)	<0.001	253 (84.6%)	<0.001

Abbreviations: GIN, gastric intraepithelial neoplasia; PGIN, proximal GIN; DGIN, distal GIN; Hp, *Helicobacter pylori*; BMI, body mass index; ETE, environmental toxin exposure; NSAIDs, nonsteroidal anti-inflammatory drugs; GERD, gastroesophageal reflux disease.

DGIN. One specific independent risk factor for PGIN was age, while that for DGIN was intake of high sodium.

Discussion

GC is a major public health problem globally,[14,15] and GIN has been well accepted as the premalignant lesion of GC.[3,16] In the present study, we comprehensively explored the clinical and pathological characteristics of GIN in the Chinese population.

The findings were as follows: 1) PGIN had half the number incidences of DGIN, but exhibited increasing trends during the study period, 2) age, FCH, less fruit intake, Hp infection, and atrophic gastritis with intestinal metaplasia were independent risk factors for GIN, and 3) age was a specific independent risk factor for PGIN, whereas that for DGIN was high sodium intake.

Emerging evidence indicated that GC could be divided into 2 categories, namely, PGC and DGC, due to different

Table 3 Univariate analysis of risk factors for early PGIN and DGIN

Variables	PGIN (n=135)		DGIN (n=299)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)				
<60	1.000 (Reference)		1.000 (Reference)	
≥60	2.265 (1.455–3.524)	0.001	1.348 (0.975–1.864)	0.070
Gender				
Female	1.000 (Reference)		1.000 (Reference)	
Male	1.422 (0.894–2.263)	0.137	1.274 (0.894–1.816)	0.180
Hp infection	3.665 (2.347–5.722)	<0.001	2.513 (1.778–3.552)	<0.001
BMI				
18.5≤ BMI ≤24.0	1.000 (Reference)		1.000 (Reference)	
BMI <18.5	1.207 (0.360–4.051)	0.760	1.172 (0.441–3.116)	0.750
24.0< BMI ≤28.0	1.428 (0.920–2.217)	0.112	1.441 (1.012–2.052)	0.143
BMI >28.0	1.358 (0.490–3.764)	0.556	1.528 (1.216–5.257)	0.437
History of cancer				
Personal	0.378 (0.045–3.171)	0.352	1.215 (0.403–3.657)	0.730
Family	2.905 (1.847–4.568)	<0.001	3.817 (2.637–5.524)	<0.001
Personal history				
ETE	0.635 (0.343–1.174)	0.148	0.900 (0.581–1.392)	0.635
Use of NSAIDs	1.439 (0.660–3.136)	0.360	0.978 (0.494–1.936)	0.949
Tobacco abuse	2.184 (1.448–3.294)	<0.001	2.265(1.637–3.135)	<0.001
Alcohol abuse	1.965 (1.305–2.959)	0.001	2.033 (1.470–2.811)	<0.001
Dietary habit				
High sodium	3.442 (2.223–5.331)	<0.001	5.603 (3.892–8.067)	<0.001
Preserved food	2.683 (1.761–4.087)	<0.001	3.450 (2.458–4.843)	<0.001
Spicy food	1.838 (1.152–2.932)	0.011	2.286 (1.556–3.358)	<0.001
Smoked food	0.614 (0.160–2.354)	0.477	0.934 (0.363–2.407)	0.888
Fried food	1.200 (0.517–2.783)	0.671	1.550 (0.796–3.018)	0.198
Hot food	1.471 (0.947–2.287)	0.086	1.258 (0.875–1.810)	0.215
Less fruit	5.246 (3.371–8.164)	<0.001	4.000 (2.860–5.593)	<0.001
Less vegetable	0.681 (0.360–1.289)	0.238	0.936 (0.593–1.477)	0.776
Present relevant illness				
Anxiety/depression status	0.834 (0.518–1.343)	0.456	0.728 (0.493–1.074)	0.109
Hypertension	1.431 (0.82–2.54)	0.119	1.242 (0.78–1.51)	0.224
Diabetes mellitus	1.161 (0.546–2.468)	0.697	1.569 (0.889–2.768)	0.120
GERD	0.771 (0.500–1.190)	0.215	0.765 (0.539–1.087)	0.135
Hiatal hernia	1.539 (0.254–9.316)	0.639	0.343 (0.036–3.320)	0.356
Columnar-lined esophagus	3.527 (0.582–21.353)	0.170	3.154 (0.631–15.750)	0.162
Gastric intestinal metaplasia and atrophy	16.591 (8.952–30.748)	<0.001	9.723 (6.581–14.366)	<0.001

Abbreviations: PGIN, proximal gastric intraepithelial neoplasia; DGIN, distal gastric intraepithelial neoplasia; OR, odds ratio; 95% CI, 95% confidential interval; Hp, *Helicobacter pylori*; BMI, body mass index; ETE, environmental toxin exposure; NSAIDs, nonsteroidal anti-inflammatory drugs; GERD, gastroesophageal reflux disease.

epidemiologic, clinicopathologic, and molecular biological characteristics.[9,10,17,18] However, recent studies challenged this classification because they found that PGC was more like DGC rather than esophageal adenocarcinoma.[19–21] Considering the existing controversy about PGC and DGC, the current study was conducted to comprehensively explore the characteristics of GC's precancerous lesion, ie, GIN, and compare the difference between PGIN and DGIN. Among all 485 patients with GIN, 329 were diagnosed with DGIN and accounted for 67.8% of the population; a similar proportion of DGC was found in all GC cases.[13,22] Furthermore, our

results showed an increasing trend for PGIN as its proportion increased gradually during the study period 2007–2014, which was similar to the trends for PGC.[23–25]

To identify risk factors for GIN, a total of 434 GIN patients with 310 well-matched controls were recruited. Based on the results of logistic regression analyses, FCH, high sodium, less fruit intake, Hp infection, and atrophic gastritis with intestinal metaplasia were identified as independent risk factors for GIN. All abovementioned parameters except Hp infection were also well documented as the risk factors for GC, which can support the conclusion that GIN

Table 4 Multivariate analysis of risk factors for PGIN and DGIN

Variables	GIN (n=434)		PGIN (n=135)		DGIN (n=299)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)						
<60	1.000 (Reference)		1.000 (Reference)		1.000 (Reference)	
≥60	0.845 (0.623–1.254)	0.087	2.001 (1.003–3.994)	0.049	1.511 (0.895–2.549)	0.122
Hp infection	2.307 (1.417–3.755)	0.001	2.057 (1.601–5.838)	0.003	2.553 (1.393–4.681)	0.002
Family history of cancer	3.485 (2.031–5.981)	<0.001	3.089 (1.515–6.300)	0.002	3.802 (2.118–6.825)	<0.001
Personal history						
Tobacco abuse	1.561 (0.883–2.759)	0.126	1.840 (0.850–3.987)	0.122	1.389 (0.754–2.558)	0.292
Alcohol abuse	0.896 (0.500–1.603)	0.711	0.872 (0.396–1.923)	0.735	0.937 (0.502–1.748)	0.838
Dietary habit						
High sodium	2.830 (1.645–4.868)	<0.001	1.840 (0.850–3.987)	0.257	3.467 (1.896–6.338)	<0.001
Preserved food	1.520 (0.894–2.584)	0.120	1.758 (0.860–3.595)	0.123	1.393 (0.783–2.479)	0.259
Spicy food	1.309 (0.752–2.280)	0.341	1.325 (0.612–2.872)	0.475	1.487 (0.812–2.722)	0.199
Less fruit	4.082 (2.515–6.625)	<0.001	4.752 (2.469–9.145)	<0.001	3.678 (2.173–6.225)	<0.001
Present relevant illness						
Gastric intestinal metaplasia and atrophy	15.070 (8.999–25.237)	<0.001	16.423 (7.513–35.898)	<0.001	14.337 (8.102–25.371)	<0.001

Abbreviations: GIN, gastric intraepithelial neoplasia; PGIN, proximal GIN; DGIN, distal GIN; OR, odds ratio; 95% CI, 95% confidential interval; Hp, *Helicobacter pylori*.

is one of the important premalignant lesions of GC to some extent.[26,27] In this study, Hp infection has been identified as an independent risk factor for GIN with an OR of 2.307 (95% CI: 1.417–3.755). Although some controversies still exist, a growing body of evidence indicated that Hp infection is etiologically related to gastric cancer, and the eradication of Hp infection could contribute to a reduced incidence of GC.[27,28] However, the detailed biological mechanisms underlying Hp infection-induced GIN remain far from understood. In addition, we also examined the association between anxiety/depression status and GIN risk; however, the results were negative. In a Chinese report including 118 patients with gastroesophageal precancerous lesions and 210 healthy controls, it was demonstrated that the anxiety and depression scale scores were higher in patients.[29]

Considering the potential variations between PGIN and DGIN, subgroup analyses were conducted. FCH, less fruit intake, Hp infection, and atrophic gastritis with intestinal metaplasia were proven as the independent risk factors for both PGIN and DGIN. In particular, age was a specific independent risk factor for PGIN while that for DGIN was intake of high sodium. The results suggested that PGIN and DGIN shared similar etiology, similar to PGC and DGC. Further studies are warranted to validate the findings.

This study comprehensively explored the potential risk factors for Chinese GIN patients in the real-world setting and found some positive results. However, some limitations should be acknowledged in interpreting the results. First, the retrospective nature might induce selection bias, even though

the study was stringently designed and conducted. Second, the limited sample size in a single institute might reduce the statistical power of the results. Third, the lost follow-up rate was relatively high (10.5%), though various efforts have been devoted and the statistical analysis showed balanced in both PGIN and DGIN groups.

Conclusion

In summary, this study provided a comprehensive overview of the clinical and pathological characteristics of GIN. FCH, high sodium intake, less fruit intake, Hp infection, and atrophic gastritis were identified as the independent risk factors for GIN. Further well-designed, prospective, and unbiased studies with a larger sample size should be conducted to verify our findings.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Detailed items and the corresponding definitions

1. Baseline information

Name:_____ Age (years):_____ Gender:_____

Operation date:____ Operation name:____ Physician name:_____

Pathology report 1: by Pathologist:_____ Date:_____

Histological type:_____ Size:_____

Macroscopic appearance:_____ Location:_____

Pathology report 2: By Pathologist:_____ Date:_____

Histological type:_____ Size:_____

Macroscopic appearance:_____ Location:_____

Helicobacter pylori (Hp) infection:_____

Note: Hp infection was determined by the rapid urease test and Giemsa stain.

Height (cm):_____ Weight (kg):_____ Body mass index (BMI):__

Note: Thin: <18.5; normal: 18.5–24.0; overweight: 24.1–28.0; obesity: >28.0.

2. History of cancer

➢ Personal cancer history (PCH):_____

➢ Family cancer history (FCH):_____

Note: FCH includes most common malignancies such as cancers in the gastrointestinal tract, lung, prostate, and breast, etc, except skin basal cell carcinoma in patients' first- and second-degree relatives.

3. Personal history

➢ Occupation:____ History of environmental toxin exposure (ETE): _____

Note: ETE was defined as a history of direct contact with toxic industrial raw materials or effluent, or living in a radius of 5 km of a heavily polluted industrious facility, or having a history of occupational toxic chemical exposure over 5 years.

➢ Alcohol abuse:_____

Note: It was defined as intake of 500 mL beer, 250 mL yellow rice wine, or 50 mL wine, over twice per week.

➢ Tobacco abuse:_____

Note: It was defined as over 10 pack/yr for tobacco abuse.

➢ Use of nonsteroidal anti-inflammatory drugs (NSAIDs):_____

Note: It was defined as long-term use due to cardiovascular or rheumatoid diseases for >6 months.

4. Dietary habit

➢ Preferences on preserved meat (≥3 times/wk):_____

➢ Preferences on spicy food (≥3 times/wk):_____

➢ Preferences on smoked food (≥3 times/wk):_____

➢ Preferences on fried food (≥3 times/wk):_____

➢ Preferences on hot food (≥3 times/wk):_____

➢ High sodium intake (defined as over 6 g daily):_____

➢ Intake of fresh fruit and vegetables (occasional, defined as <2/wk):_

5. Present relevant illness

➢ Gastroesophageal reflux disease (GERD):_____

Note: GERD was defined as symptoms of acid reflux such as heartburn and laryngopharyngeal reflux.

➢ Hypertension (>5 years):_____

➢ Diabetes mellitus (>5 years):_____

➢ Hiatal hernia (sliding and/or mixed types):_____

➢ Anxiety/depression status:_____

Note: Anxiety status was determined with Zung Self-Rating Anxiety Scale, while depression status was examined with Zung Self-Rating Depression Scale.