

Risk factors for gastric cancer: a large-scale, population-based case-control study

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Abstract

Background: Early detection of gastric cancer (GC) has been the topic of major efforts in China. This study aimed to explore the risk factors associated with GC and to provide evidence for the selection of a high-risk population of GC.

Methods: Based on the cancer screening cohort of the National Cancer Screening Program in Urban China, GC patients diagnosed by endoscopy and pathological examinations constituted the case group, and controls were 1:3 matched by sex and age (± 5 years) individually. The variables were selected by univariable analysis of factors such as body mass index (BMI), dietary habits, lifestyle, stomach disease history, and family history of GC; and multivariable logistic regression was used to analyze the influencing factors of GC and to calculate the odds ratio (OR) of related factors and its 95% confidence interval (CI).

Results: A total of 215 GC cases and 645 matched healthy controls were included in the final analysis, with a median age of 61 years for the case and control groups. Overall analysis showed that high educational level (above primary school) (OR = 0.362, 95% CI = 0.219–0.599, $P < 0.001$), overweight/obesity (BMI ≥ 24 kg/m²; OR = 0.489, 95% CI = 0.329–0.726, $P < 0.001$), cigarette smoking (OR = 3.069, 95% CI = 1.700–5.540, $P < 0.001$), alcohol consumption (OR = 1.661, 95% CI = 1.028–2.683, $P = 0.038$), history of stomach disease (OR = 6.917, 95% CI = 4.594–10.416, $P < 0.001$), and family history of GC in first-degree relatives (OR = 4.291, 95% CI = 1.661–11.084, $P = 0.003$) were significantly correlated with the occurrence of GC. Subgroup analyses by age and gender indicated that GC risk was still increased in the presence of a history of stomach disease. A history of chronic gastritis, gastric ulcer, or gastric polyposis was positively associated with GC, with adjusted ORs of 4.155 (95% CI = 2.711–6.368), 1.839 (95% CI = 1.028–3.288), and 2.752 (95% CI = 1.197–6.326).

Conclusions: Subjects who smoke, drink, with history of stomach disease and family history of GC in first-degree relatives are the high-risk populations for GC. Therefore, attention should be paid to these subjects for GC screening.

Keywords: Risk factors; Gastric cancer; Case-control study; Cancer screening

Introduction

Gastric cancer (GC) is one of the most common types of upper gastrointestinal cancer in China. According to the latest report from the International Agency for Research on Cancer,^[1] there were 479,000 new cases and 374,000 deaths due to GC in China in 2020, accounting for 44.0% and 48.6%, respectively, of the global new cases and deaths due to GC. In the past 10 years, although the incidence and mortality rates for GC have shown a downward trend in China, it still ranks fourth in the incidence of malignant tumors, and its mortality ranks third, which seriously threatens the lives and health of people in China.^[1-2]

Because the clinical symptoms of early GC are not obvious, most patients are in the middle or late stages when they are diagnosed. The clinical treatment costs are high, with poor outcomes, and the survival period is brief. According to the latest data,^[3] the 5-year survival rate for GC is 35.1% in China. When GC is discovered at an early stage and properly treated, the 5-year survival rate can exceed 90%.

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sometimes achieving complete remission. Therefore, prevention and timely diagnosis are crucial to improve the prognosis of GC. However, due to the multidimensional nature of GC, prevention is subject to accurate identification of the risk factors and underlying causes of this disease, as well as the management of these factors.^[4]

In view of the increasing burden of cancer among urban populations in China, the Ministry of Finance and the previous Ministry of Health of China approved the urban cancer early diagnosis and treatment project in 2012 to carry out assessments of high-risk populations and clinical screening for six major types of cancers, including GC. Based on the screening population of this project, a case-control study was conducted to explore the risk factors affecting the occurrence of GC and provide a scientific basis for the design of GC screening strategies in China's urban population.

Methods

Ethical approval

The study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College, Beijing, China (No.15-070/997). Informed consent was obtained from all participants before enrollment.

Study population

The study was based on a large-scale, multicenter cancer screening cohort in urban areas of China. Subjects who were 40 to 74 years old, had no serious organ dysfunction or mental illness, and had been living in the current location for at least 3 years were eligible to participate in

the screening program. Altogether 3,808,459 participants were enrolled and completed the questionnaire in 22 provinces between September 2012 and December 2019. After filling the questionnaire, 678,214 high-risk individuals of GC were selected through the risk assessment model and they were recommended to go to designated hospitals for free gastroscopy. Among them, 100,138 subjects accepted gastroscopy and pathological examinations, and 215 GC patients were diagnosed. All endoscopic examinations were conducted by well-trained endoscopy doctors at local hospitals according to the protocol for cancer screening in urban areas of China. Then, pathologists independently read the biopsy slides. Control subjects were selected from the general population who filled in the questionnaire and individually matched at a ratio of 1:3 by sex and age (± 5 years). There were 215 patients in the case group, and there were 645 subjects in the control group [Figure 1].

Data collection

All study interviews were conducted face-to-face by highly trained investigators. A structured questionnaire consisting of five categories of questions was used for data collection. The questionnaires included the following categories: (1) general demographic information, including age, gender, height, weight, marital status, and educational level; (2) dietary habits, including the intake of fresh fruits and vegetables, preference of food temperature, taste preference of diet, and pickled foods; (3) lifestyle factors, including cigarette smoking, alcohol consumption, and physical activity; (4) history of stomach disease, including chronic gastritis, gastric ulcer, duodenal ulcer, gastric polyposis, remnant stomach, dysplasia, and intestinal metaplasia; and (5) family history of GC (FHGC) in first-degree relatives.

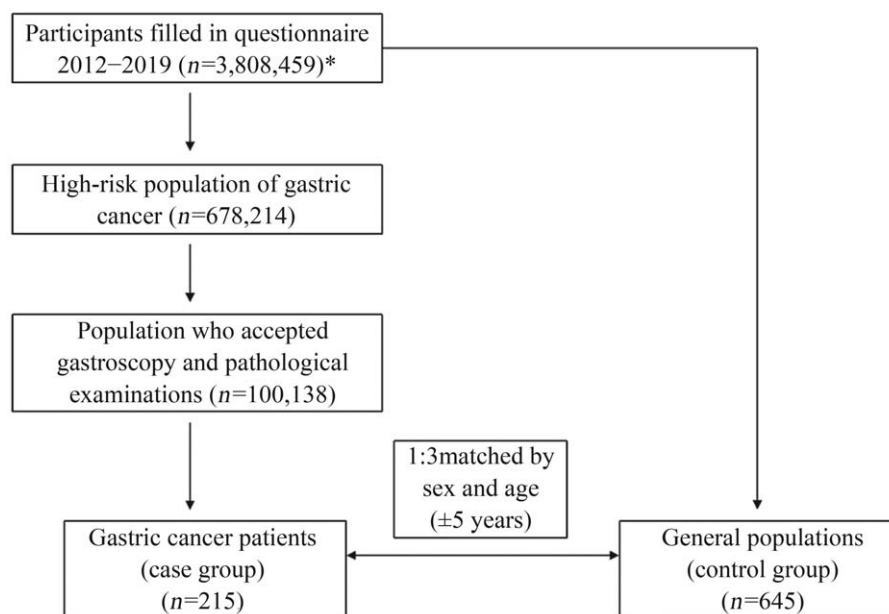


Figure 1: Flowchart for the selection of the case and control subjects. * Participants came from 22 provinces, including Anhui, Beijing, Gansu, Guangdong, Guangxi, Hainan, Hebei, Henan, Heilongjiang, Hubei, Hunan, Jiangsu, Jiangxi, Liaoning, Inner Mongolia, Shandong, Shanxi, Shaanxi, Xinjiang, Yunnan, Zhejiang, and Chongqing.

Regarding dietary habits, the intake of fruits and vegetables was measured as the intake frequency or the average personal intake in the last 2 years, which was calculated by dividing the total intake of household by the number of a family member and calculated by the weight of uncooked (fresh fruits were not peeled). Frequent fruits and vegetable intake was defined as >3 days/week or >2500 g/week for vegetables and >1250 g/week for fruits. Pickled food included salted fish, sauerkraut, and pickles, and frequent intake was defined as consuming >4 days/week. Participants were defined as smokers if they had smoked at least one cigarette per day during the previous 6 months. Alcohol consumption was defined as drinking alcoholic beverages at least once per week during the previous 6 months. Regular physical activity was defined as exercising for >30 min at least three times per week. History of stomach disease includes chronic gastritis, gastric ulcer, duodenal ulcer, gastric polyposis, remnant stomach, gastric mucosal intraepithelial neoplasia, and gastrointestinal epithelial metaplasia, which were examined at a formal medical institution with corresponding examination conditions and diagnostic capabilities, as well as confirmed by a practicing physician. FHGC in first-degree relatives was defined as having a first-degree relative at least (*ie*, a parent or child of the participant) who was diagnosed with stomach cancer. According to the standard recommended by the guidelines for the prevention and control of overweight and obesity in adults in China,^[5] body mass index (BMI) < 18.5 kg/m² means low weight, 18.5 to 23.9 kg/m² means normal weight, and BMI ≥24.0 kg/m² means overweight and obesity.

Statistical analysis

SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. When the continuous variables met the criteria for normality and homogeneity of variance, they were expressed as mean ± standard deviation, and Student's *t* test was performed to compare the case and control groups. Otherwise, continuous variables were expressed as median (P_{25} , P_{75}) and compared using the Wilcoxon signed-rank test. The categorical variables were expressed as percentages and compared using the Chi-square or Fisher's exact test. To assess the risk factors for GC, conditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs). All variables related to GC at a significance level according to the univariable conditional logistic analysis were included in the multivariable conditional logistic regression analysis. Moreover, subgroup analysis by age and gender was performed to evaluate the relationship between history of stomach disease and GC. All reported *P*-values were two-tailed, and $P < 0.05$ were considered statistically significant.

Results

The distributions of basic characteristics of the study participants are shown in Table 1. Because case and control groups were individually matched on age (±5 years) and gender, the median age of the two groups was 61 years old. Fifty-eight percent of the study participants were male, and approximately 99% of

participants were married. Differences in educational level, BMI, taste preference of diet, pickled food intake, cigarette smoking, alcohol consumption, physical activity, history of stomach disease, and FHGC in first-degree relatives between the case and control groups were statistically significant ($P < 0.05$).

All variables related to GC at a significance level of $P < 0.05$ according to the univariable analysis were included in the multivariate conditional logistic regression analysis. The ORs of major factors significantly and marginally associated with GC are shown in Table 2. Educational level was inversely associated with GC risk (above primary school *vs.* primary school and below: OR = 0.362, 95% CI = 0.219–0.599). Overweight/obesity (BMI ≥24 kg/m²) had a protective effect on GC risk compared with normal/lean weight, with an OR of 0.489 (95% CI = 0.329–0.726). The OR for smokers *vs.* never-smokers was 3.069 (95% CI = 1.700–5.540). The OR for drinkers *vs.* never-drinkers was 1.661 (95% CI = 1.028–2.683). GC risk was increased in the presence of a history of stomach disease (OR = 6.917, 95% CI = 4.594–10.416) and FHGC in first-degree relatives (OR = 4.291, 95% CI = 1.661–11.084).

Table 3 shows the results of subgroup analysis of the association between a history of stomach disease and GC risk by age and gender. GC risk was increased in the presence of a history of stomach disease in different subgroups.

Stomach disease included chronic gastritis, gastric ulcer, duodenal ulcer, gastric polyposis, remnant stomach, dysplasia, and intestinal metaplasia. We did not analyze the association between a history of dysplasia, as well as intestinal metaplasia, and GC risk due to the limited number of patients in case group and subjects in the control group. However, a history of chronic gastritis, gastric ulcer, or gastric polyposis was positively associated with GC, with adjusted ORs of 4.155 (95% CI = 2.711–6.368), 1.839 (95% CI = 1.028–3.288), and 2.752 (95% CI = 1.197–6.326) [Table 4].

Discussion

In this study, based on a population in urban areas of China, cigarette smoking, alcohol consumption, history of stomach disease, and FHGC in first-degree relatives were identified as the factors to increase the risk of GC. However, overweight and obesity (BMI ≥24 kg/m²) and high educational level were inversely associated with the risk of GC.

Educational level and income, which are the most important determinants of social class, are directly related to the level of health.^[6] Although educational attainment alone cannot directly affect GC risk, it can affect some GC risk factors, including *Helicobacter pylori* infection, which play a role in the development of GC. In our study, educational level was inversely associated with GC risk (above primary school *vs.* primary school and below: OR = 0.362, 95% CI = 0.219–0.599). The result of a

Table 1: Comparison of basic characteristics of the case and control groups from the National Cancer Screening Program in Urban China.

Parameters	Case group (n = 215)	Control group (n = 645)	Chi-square value	P value
Age, years	61 (55, 66)	61 (55, 66)	–	–
Gender			–	–
Male	125 (58.14)	375 (58.14)		
Female	90 (41.86)	270 (41.86)		
BMI (kg/m ²)*			17.284	<0.001
<24.0	105 (48.84)	213 (33.02)		
≥24.0	110 (51.16)	432 (66.98)		
Educational level			18.236	<0.001
Primary school and below	59 (27.44)	94 (14.57)		
Above primary school	156 (72.56)	551 (85.43)		
Marital status			–†	0.050
Unmarried	3 (1.40)	1 (0.16)		
Married	212 (98.60)	644 (99.84)		
Fruits and vegetables intake			14.049	<0.001
Not frequent	162 (75.35)	395 (61.24)		
Frequent	53 (24.65)	250 (38.76)		
Preference of food temperature			22.690	<0.001
Not hot	127 (59.07)	490 (75.97)		
Hot	88 (40.93)	155 (24.03)		
Taste preference of diet			32.857	<0.001
Mild or low salt	112 (52.09)	472 (73.18)		
High salt	103 (47.91)	173 (26.82)		
Pickled food intake			20.132	<0.001
Not frequent	151 (70.23)	543 (84.19)		
Frequent	64 (29.77)	102 (15.81)		
Cigarette smoking			53.186	<0.001
No	101 (46.98)	477 (73.95)		
Yes	114 (53.02)	168 (26.05)		
Alcohol consumption			50.192	<0.001
No	94 (43.72)	455 (70.54)		
Yes	121 (56.28)	190 (29.46)		
Physical activity			12.308	<0.001
Not frequent	136 (63.26)	319 (49.46)		
Frequent	79 (36.74)	326 (50.54)		
History of stomach disease			192.653	<0.001
No	64 (29.77)	521 (80.78)		
Yes	151 (70.23)	124 (19.22)		
FHGC‡			28.319	<0.001
No	196 (91.16)	636 (98.6)		
Yes	19 (8.84)	9 (1.40)		

Data are presented as median ($P_{2.5}, P_{7.5}$) or n (%). BMI: Body mass index; FHGC: Family history of GC. * Since subjects with BMI < 18.5 kg/m² are few, therefore it was merged into the normal weight group and recorded as BMI < 24.0 kg/m². † The variable marital status did not meet the application conditions of the chi-square test, which a grid theoretical frequency was <1, so Fisher’s exact test was used. ‡ FHGC in first-degree relatives.

meta-analysis conducted by Bonequi *et al*^[7] showed that higher educational levels and GC had a significant inverse correlation and was associated with a 52% decrease in GC risk. These findings were consistent with the results of our study.

Our study observed that GC was associated with cigarette smoking, and the OR for smokers *vs.* never smokers was 3.069 (95% CI = 1.700–5.540). In 2004, a report jointly published by the Office of the Surgeon General (US) and the Office on Smoking and Health (US), stated that based on research evidence, smoking had a causal relationship with GC.^[8] Many meta-analyses have revealed a positive association between cigarette smoking and GC.^[9–11]

Poorolajal *et al*^[9] conducted a meta-analysis that included 77 studies published between 1985 and 2018; the results indicated that current smokers and former smokers were at higher risk of GC than non-smokers (OR = 1.610, 95% CI = 1.490–1.750 and OR = 1.430, 95% CI = 1.290–1.590, respectively).

Many studies have reported that alcohol consumption is another risk factor for GC.^[6,12,13] The result of a meta-analysis performed by Poorolajal *et al*^[9] revealed that GC risk was higher in drinkers than in never-drinkers (OR = 1.190, 95% CI = 1.100–1.290). Concerning the effects of alcohol consumption on GC risk, it can be said that alcohol created a cancer-stimulating mechanism that

Table 2: Association between potential factors and GC in multivariate conditional logistic regression analysis.

Parameters	β	Standard error	Wald χ^2	P-value	OR	95% CI
Educational level						
Primary school and below <i>vs.</i> above primary school	-0.508	0.129	15.604	<0.001	0.362	0.219–0.599
BMI (kg/m ²)						
≥ 24 <i>vs.</i> <24	-0.358	0.101	12.566	<0.001	0.489	0.329–0.726
Fruits and vegetables intake						
Frequent <i>vs.</i> not frequent	-0.104	0.114	0.843	0.359	0.812	0.520–1.267
Preference of food temperature						
Hot <i>vs.</i> not hot	0.037	0.110	0.113	0.737	1.077	0.699–1.657
Taste preference of diet						
High salt <i>vs.</i> mild or low salt	-0.001	0.118	<0.001	0.994	0.998	0.630–1.582
Pickled food intake						
Frequent <i>vs.</i> not frequent	0.020	0.128	0.024	0.877	1.040	0.629–1.720
Cigarette smoking						
Yes <i>vs.</i> no	0.561	0.151	13.839	<0.001	3.069	1.700–5.540
Alcohol consumption						
Yes <i>vs.</i> no	0.254	0.122	4.293	0.038	1.661	1.028–2.683
Physical activity						
Frequent <i>vs.</i> not frequent	-0.102	0.101	1.010	0.315	0.816	0.549–1.213
FHGC in first-degree relatives						
Yes <i>vs.</i> no	0.728	0.242	9.045	0.003	4.291	1.661–11.084
History of stomach disease						
Yes <i>vs.</i> no	0.967	0.104	85.773	<0.001	6.917	4.594–10.416

CI: Confidence interval; FHGC: Family history of GC; GC: Gastric cancer; OR: Odds ratio. Frequent fruits and vegetables intake: >3 days/week or >2500 g/week for vegetables and >1250 g/week for fruits. Frequent pickled food intake: >4 days/week. Frequent physical activity: >3 times/week and >30 minutes per time.

Table 3: Subgroup analysis by age and gender for the case and control groups from the National Cancer Screening Program in Urban China.

History of stomach disease	Case group (n = 215)		Control group (n = 645)		OR*	95% CI	OR†	95% CI
	N	%	N	%				
Male, age ≤ 60 years								
No	15	28.85	126	80.77	1.000	–	1.000	–
Yes	37	71.15	30	19.23	9.870	4.821–20.206	5.691	2.327–13.917
Male, age >60 years								
No	22	30.14	188	85.84	1.000	–	1.000	–
Yes	51	69.86	31	14.16	14.314	7.451–27.500	11.031	5.075–23.973
Female, age ≤ 60 years								
No	12	27.27	98	74.24	1.000	–	1.000	–
Yes	32	72.73	34	25.76	7.189	3.365–15.360	8.622	3.170–23.448
Female, age >60 years								
No	15	32.61	109	78.99	1.000	–	1.000	–
Yes	31	67.39	29	21.01	8.135	3.737–17.710	5.396	2.141–13.603

* Adjusted for age and gender. † Adjusted for age, gender, educational level, BMI, salt intake, pickled food intake, cigarette smoking, alcohol consumption, physical activity, and FHGC. BMI: Body mass index; CI: Confidence interval; FHGC: Family history of GC; OR: Odds ratio.

involved a chronic inflammatory response to the toxic effects of ethanol metabolites and cytokines and, thus, the increased exposure of nitrosamines.^[14]

Chen *et al*^[15] conducted a meta-analysis of 24 prospective studies with 41,791 cases published before 2013 to evaluate the association between GC and BMI. Overall, both overweight (BMI = 25–30 kg/m²) and obesity (BMI ≥ 30 kg/m²) showed a protective but non-significant

association with stomach cancer [overweight: summary relative risks (SRR) = 1.01, 95% CI = 0.960–1.070; obesity: SRR = 1.06, 95% CI = 0.990–1.120]. However, we found that overweight and obesity (BMI ≥ 24 kg/m²) was the protective factor for GC compared with normal/low weight (OR = 0.489, 95% CI = 0.329–0.726). This discrepancy could be due to the small sample size or unavailability of data regarding *H. pylori* infection in the study participants.

Table 4: Association between specific stomach diseases and GC risk.

History of stomach disease	Case group		Control group		OR*	95% CI	OR†	95% CI
	N	%	N	%				
Chronic gastritis								
No	84	39.07	543	84.19	1.000	–	1.000	–
Yes	131	60.93	102	15.81	8.271	5.810–11.773	4.155	2.711–6.368
Gastric ulcer								
No	145	67.44	601	93.18	1.000	–	1.000	–
Yes	70	32.56	44	6.82	7.451	4.770–11.640	1.839	1.028–3.288
Duodenal ulcer								
No	179	83.26	627	97.21	1.000	–	1.000	–
Yes	36	16.74	18	2.79	7.172	3.952–13.018	1.857	0.873–3.949
Gastric polyposis								
No	181	84.19	631	97.83	1.000	–	1.000	–
Yes	34	15.81	14	2.17	9.269	4.730–18.165	2.752	1.197– 6.326
Remnant stomach								
No	208	96.74	643	99.69	1.000	–	1.000	–
Yes	7	3.26	2	0.31	10.883	2.238–52.931	1.300	0.194–8.709

* Adjusted for age and gender. † Adjusted for age, gender, educational level, BMI, salt habit, pickled food, cigarette smoking, alcohol consumption, physical activity, and FHGC. CI: Confidence interval; BMI: Body mass index; FHGC: Family history of GC; GC: Gastric cancer; OR: Odds ratio.

Having a FHGC in first-degree relatives was also found to be a strong potential risk factor for GC in this study (OR = 4.291, 95% CI = 1.661–11.084). Having a first-degree relative with GC was a consistent risk factor for GC, although the magnitude of the OR associated with a positive family history varied depending on the ethnic group and geographic region, ranging from 2 to 10.^[16,17]

Based on our study, having a history of stomach disease dramatically increased GC risk in fully adjusted regression models (OR = 6.917, 95% CI = 4.594–10.416). Furthermore, the elevated risk remained when a subgroup analysis was conducted for age and gender, with ORs ranging from 7 to 14 when adjusted for age and gender and from 5 to 11 when adjusted for all variables. For specific stomach diseases, chronic gastritis, gastric ulcer, and gastric polyposis showed increased GC risk in age- and gender-adjusted and fully adjusted regression models. An association between history of stomach disease and GC was reported in two previous studies.^[18,19] In a cohort study, Sadjadi *et al*^[18] found that a history of gastric ulcer was a strong risk determinant [hazard ratio (HR) = 9.00, 95% CI = 3.30–24.80] in fully adjusted Cox regression model. People with a history of atrophic gastritis had a higher risk for GC. Moreover, GC risk was positively correlated with atrophic gastritis severity (mild: HR = 2.08, 95% CI = 0.74–5.80; moderate: HR = 3.60, 95% CI = 1.14–11.34; marked: HR = 6.77, 95% CI = 1.62–28.43; $P_{trend} = 0.036$), which is consistent with the results of our study.

Many studies have revealed that diet and dietary habits (*eg*, inadequate fresh fruit and vegetable intake and excessive salt and pickled food intake) are the risk factors of GC.^[6,9] The anti-carcinogenic effects of fruits and vegetables may be attributed to the antioxidant effect of their vitamin content, especially vitamin C and beta-carotene. Antioxidants neutralize reactive oxygen free radicals, which cause

DNA damage.^[20] Pickled food may increase the risk of GC because they contain large amounts of salt and key nutrients are lost in food under acidic and oxygenic conditions.^[21,22] Furthermore, pickled vegetables are considered to be a possible source of nitrosamines, which may contribute to GC. Excessive salt consumption might act as a gastric mucosa stimulant, leading to atrophic gastritis, increased DNA synthesis, and cell proliferation, thereby providing the basis for the development of GC.^[13] Our study showed that these dietary habits may increase GC risk, but the association was non-significant ($P > 0.05$). A possible explanation was the inaccurate calculation of dietary frequency and the existence of confounding factors.

The strengths of this study are that it is a case-control study, based on the large-scale cancer screening cohort of the National Cancer Screening Program in Urban China, as well as the relationship between the history of different types of gastric diseases and the risk of GC has been explored. One of the limitations of this study is that the risk factors for different types of GC, including cardia and non-cardia cancer, may be different. Therefore, focusing on the risk factors for each type of GC is suggested in future studies.

This study found that cigarette smoking, alcohol consumption, FHGC in first-degree relatives, and history of stomach disease, including chronic gastritis, gastric ulcer, and gastric polyposis, increased GC risk. Individuals with these potential risk factors should therefore be considered a high-risk population in urban areas of China.

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Conflicts of interest

None.

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