

Body mass index, serum total cholesterol, and risk of gastric high-grade dysplasia

A case–control study among Chinese adults

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Abstract

Obesity is related to an increased risk of gastric cardia cancer. However, the influences of excess body weight and serum total cholesterol on the risk of gastric high-grade dysplasia have not been fully characterized.

A case–control study was conducted to explore the relationships between body mass index (BMI), serum total cholesterol level, and the risk of gastric high-grade dysplasia in Chinese adults. A total of 893 consecutive patients with gastric high-grade dysplasia (537 men and 356 women) and 902 controls (543 men and 359 women) were enrolled from January 2000 to October 2015. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated, and a multivariate analysis was conducted.

After adjusting for age, alcohol consumption, smoking status, family history of gastric cancer or esophageal cancer, and serum total cholesterol level, a BMI ranging from 27.5 to 29.9 was significantly related to an increased risk of gastric high-grade dysplasia in both men (adjusted OR=1.87, 95% CI=1.24–2.81) and women (adjusted OR=2.72, 95% CI=1.44–5.16). The 2 highest BMI categories (27.5–29.9 and ≥ 30.0) were identified as risk factors for gastric cardia high-grade dysplasia in both men (BMI=27.5–29.9: adjusted OR=1.78, 95% CI=1.02–3.10; BMI ≥ 30.0 : adjusted OR=2.54, 95% CI=1.27–5.08) and women (BMI=27.5–29.9: adjusted OR=2.88, 95% CI=1.27–6.55; BMI ≥ 30.0 : adjusted OR=2.77, 95% CI=1.36–5.64), whereas only a BMI ranging from 27.5 to 29.9 was a risk factor for gastric noncardia high-grade dysplasia in both men (adjusted OR=1.98, 95% CI=1.25–3.14) and women (adjusted OR=2.88, 95% CI=1.43–5.81). In addition, higher serum total cholesterol was associated with an increased risk of gastric noncardia high-grade dysplasia (adjusted OR=1.83, 95% CI=1.25–2.69) in women.

Increased BMI was associated with an increased risk of gastric high-grade dysplasia in both men and women, and higher serum total cholesterol increased the risk of gastric noncardia high-grade dysplasia in women.

Abbreviations: BMI = body mass index, GC = gastric cancer, HDL = high-density lipoprotein, OR = odds ratio, WHO = World Health Organization.

Keywords: body mass index, gastric high-grade dysplasia, serum total cholesterol

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1. Introduction

Gastric cancer (GC) was the fifth most common cancer and the third leading cause of cancer-related mortality worldwide in 2012; specifically, it was responsible for 723,000 deaths that year.^[1,2] GC is a multifactorial disease, and both genetic and environmental factors are involved in its etiology. Risk factors for the noncardia and cardia regions of the stomach might differ. Common risk factors for both noncardia and cardia GC included the male sex,^[3] older age,^[4] radiation exposure,^[5] cigarette smoking,^[6] and a family history of GC.^[7,8] Factors related to noncardia GC, but not cardia GC, included *Helicobacter pylori* infection,^[9] low socioeconomic status,^[10] and possible dietary factors such as the high intake of smoked and salty food and the low consumption of vegetables and fruits.^[11–13] Risk factors that are exclusive to cardia GC include gastroesophageal reflux disease^[14,15] and obesity.^[16,17]

Atrophic gastritis, intestinal metaplasia, and gastric dysplasia are histologic premalignant lesions found to be multistep cascade precursors of gastric carcinogenesis.^[18] Of these lesions, gastric dysplasia (especially gastric high-grade dysplasia) might be the last stage before GC development.^[19] The Vienna classification of gastrointestinal epithelial neoplasia was the first source to clarify gastric high-grade dysplasia, and it has helpfully resolved many of the discrepancies between Western and Japanese

pathologists regarding the diagnosis of gastrointestinal epithelial neoplastic lesions.^[20] Approximately 85% of all patients with gastric dysplasia progress to GC annually^[21,22]; however, the risk factors for gastric high-grade dysplasia are not well characterized.

Obesity is defined as “abnormal or excessive fat accumulation to the extent that health is impaired,” and it is the fastest growing lethal disease in the Western and developing worlds.^[23] The World Health Organization (WHO) estimated that more than 1.9 billion adults, 18 years old and older, were overweight worldwide in 2014. Of these individuals, over 600 million were obese. Obesity is associated with increased risks of various types of cancer including breast,^[24] endometrium,^[25] ovary,^[26] colorectal,^[27] esophageal,^[28] liver,^[29] gallbladder, pancreatic,^[30] kidney,^[31] and stomach cancer.^[32] The relationship between obesity and GC was implicated through the positive association with cardia GC (but not noncardia GC) observed in several meta-analyses. Obesity was also related to an increased risk of early GC (both cardia and noncardia cancers) in a recent case-control study.^[32] High serum cholesterol levels are a major risk factor for cardiovascular disease.^[33] In addition, prospective and cross-sectional studies have suggested that an association exists between low serum cholesterol levels and subsequent cancer mortality.^[34] Subsequently, low serum cholesterol levels were found to be an independent risk factor for GC, especially intestinal-type GC.^[35] However, the effects of obesity and serum cholesterol levels on the incidence of gastric high-grade dysplasia have not been well elucidated.

We conducted a retrospective investigation among Chinese adults to determine the relations between body mass index (BMI), an acceptable proxy for thinness and fatness, and the risk of gastric high-grade dysplasia. The association of serum total cholesterol level and the risk of gastric high-grade dysplasia was also examined. To determine whether BMI or serum total cholesterol level was related to the risk of gastric high-grade dysplasia at different sites such as gastric cardia or noncardia high-grade dysplasia, subgroup analysis was performed.

2. Materials and methods

2.1. Study subjects

A retrospective, hospital-based, case-control study was conducted. Patients histologically diagnosed with gastric high-grade dysplasia were enrolled at Peking Union Medical College Hospital from January 2000 to October 2015. All patients with gastric high-grade dysplasia were histologically confirmed via endoscopic submucosal dissection or surgical specimen according to the Vienna classification of gastrointestinal epithelial neoplasia.^[20] Patients were excluded as cases if they required prompt medical care, the site of the primary tumor was unknown, they had previously undergone gastric resection, they had a history of any type of wasting disease before the diagnosis of gastric high-grade dysplasia, or they had a history of cancer or concurrent cancer. The participants undergoing endoscopy who were free of cancer and any evidence of gastric dysplasia, atrophic gastritis, mucosa-associated lymphoid tissue lymphoma, or any type of wasting disease were recruited to the control groups. The controls were frequency matched by the sex and age (within 3 years) of the patients.

All of the participants provided written informed consent before enrolment and completed a questionnaire that included information on typical body weight and height over the last 3

years; a history of hypolipidemic therapy; demographic characteristics; *H pylori* infection status; personal and family histories of GC and other diseases; smoking and alcohol consumption habits; and environmental, occupational, and dietary exposures. Smoking status was classified into 2 categories: never smoked and smokers, the latter of which included former smokers and current smokers. Participants were also divided into 2 groups by drinking status: drinkers and never/rare drinkers. The Ethics Committee of Peking Union Medical College Hospital approved this study (S-k056).

2.2. Body mass index

BMI, a measure of adiposity, was calculated as weight in kilograms divided by height in meters squared (kg/m^2). The heights and weights of patients were measured at hospital admission; these variables were measured for controls when they underwent endoscopy. The typical body weights and heights of all participants who lost weight over the last 3 years were collected before weight loss. BMIs were categorized as follows: 18.4 or lower, 18.5 to 22.9, 23.0 to 27.4, 27.5 to 29.9, and 30.0 or more.^[36] These categories are more suitable for Asia-Pacific populations than those proposed by the WHO.^[37] For our analyses and discussion, the range from 23.0 to 27.4 was referred to as “overweight”; that from 27.5 to 29.9 corresponded to “obese”; and values of 30.0 or more were referred to as “severely obese.” The BMI category ranging from 18.5 to 22.9 was considered as the reference group for all primary analyses.

2.3. Gastric high-grade dysplasia

A pathologist confirmed all of the cases diagnosed as gastric high-grade dysplasia based on the Vienna classification of gastrointestinal epithelial neoplasia. High-grade dysplasia denoted a group of lesions with features more severe than those considered as low-grade dysplasia but without evidential invasion^[19] that included high-grade adenoma or dysplasia, noninvasive carcinoma (carcinoma in situ), and suspicion of invasive carcinoma. Neoplasia sites were identified via anatomic site, and gastric cardia high-grade dysplasia was defined as neoplasia located within 2 cm of the gastroesophageal junction. Neoplasia originating from the distal stomach was identified as gastric noncardia high-grade dysplasia.^[32]

2.4. Serum total cholesterol determination

Fasting blood samples were taken from the patients at hospital admission and from controls at endoscopy. Serum total cholesterol was measured enzymatically using an analyser (AU5800, Beckman Coulter, Brea, CA). The typical serum total cholesterol of all participants who lost weight over the last 3 years or received hypolipidemic therapy were collected before weight loss or hypolipidemic therapy. The participants were divided into 2 groups based on serum total cholesterol level according to the largest Yueden index: ≤ 4.55 or > 4.55 mmol/L.

2.5. Information on covariates

Potential confounders included in data analyses were age (in single years), smoking status (never smoked and smokers, the latter of which included former smokers and current smokers), alcohol consumption (drinkers and never/rare drinkers), and family history of GC or esophageal cancer.

Table 1**Characteristics of male patients and controls.**

	Gastric high-grade dysplasia (n=537)	Control (n=546)	P
Age, y, mean ± SD	60.75 ± 10.26	59.95 ± 10.04	0.198
Age categories, y			
≤39	12	14	
40–49	61	62	
50–59	161	161	
60–69	208	218	
≥70	95	91	
Weight, kg, mean ± SD	72.92 ± 10.54	72.16 ± 9.76	0.194
Height, m, mean ± SD	1.70 ± 0.06	1.74 ± 0.10	≤0.001
BMI, kg/m ² , mean ± SD	25.22 ± 3.36	24.57 ± 3.04	0.001
Cholesterol level, mmol/L	4.58 ± 0.93	4.48 ± 0.96	0.083
Alcohol use			0.114
Drinker	155	134	
Never drinks/rare drinker	382	412	
Smoking status			0.670
Former smoker/current smoker	259	256	
Never smoked	278	290	
Family history of gastric cancer or esophagus cancer			≤0.001
Yes	70	21	
No	467	525	

BMI=body mass index, SD=standard deviation.

2.6. Statistical analyses

The associations between potential confounds and gastric high-grade dysplasia risk were assessed using chi-squared tests and Student *t* tests. The potential confounds included age, alcohol use, smoking status, and family history of GC or esophageal cancer (for gastric cardia high-grade dysplasia only). Univariate and multivariate logistic regression models were used to generate odds ratios (ORs) with corresponding 95% confidence intervals (CI) regarding BMI classifications and serum total cholesterol. The multivariate analyses were performed using multivariate logistic regression models to adjust for the following potential confounds with regard to all estimates of risk: age, alcohol consumption, smoking status, family history of GC or esophageal cancer, serum total cholesterol, and BMI. All statistical tests were 2-tailed, and the significance threshold was set at $\alpha = 0.05$. All analyses were performed using SPSS 20.0^[38] (IBM, Armonk, NY). With a sample of 893 patients and an expected OR of 1.7, we estimated that the trial would have 98% overall power to show a between-group difference in the primary outcome.

3. Results

3.1. Participant characteristics

In total, 893 consecutive patients with gastric high-grade dysplasia (537 men and 356 women) and 902 controls (543 men and 359 women) were enrolled in the present study. The baseline characteristics of the patients with gastric high-grade dysplasia and the controls are depicted in Tables 1 and 2. The mean age of patients was 60.75 years for men and 59.44 years for women, whereas the controls had mean ages of 59.95 years for men and 58.87 years for women. In men, the serum total cholesterol levels were 4.58 ± 0.93 and 4.48 ± 0.96 mmol/L for patients and controls, respectively. The women with gastric high-grade dysplasia had a serum total cholesterol level of 4.91 ± 0.97 mmol/L, whereas the serum total cholesterol level of healthy women was 4.74 ± 0.89

Table 2**Characteristics of female patients and controls.**

	Gastric high-grade dysplasia (n=356)	Control (n=359)	P
Age, y, mean ± SD	59.44 ± 11.96	58.87 ± 12.60	0.538
Age categories, y			
≤39	31	34	
40–49	38	32	
50–59	85	98	
60–69	123	114	
≥70	79	81	
Weight, kg, mean ± SD	63.66 ± 10.74	60.25 ± 9.40	0.001
Height, m, mean ± SD	1.60 ± 0.05	1.59 ± 0.04	0.001
BMI, kg/m ² , mean ± SD	24.69 ± 3.63	23.75 ± 3.52	≤0.001
Cholesterol level, mmol/L	4.91 ± 0.97	4.74 ± 0.89	0.013
Alcohol use			0.021
Drinker	10	2	
Never drinks/rare drinker	346	357	
Smoking status			0.001
Former smoker/current smoker	18	2	
Never smoked	338	357	
Family history of gastric cancer or esophagus cancer			0.001
Yes	50	8	
No	306	351	

BMI=body mass index, SD=standard deviation.

mmol/L. Both male and female patients were more likely to have family histories of GC or esophageal cancer than their respective controls. However, women with gastric high-grade dysplasia were more likely to drink and smoke. Men with gastric high-grade dysplasia showed significantly higher BMIs (25.22 ± 3.36 kg/m²) than their respective controls (24.57 ± 3.04 kg/m², $P = 0.001$). Women with gastric high-grade dysplasia significantly differed from controls with regard to BMI (24.69 ± 3.63 kg/m² for patients vs 23.75 ± 3.52 kg/m² for controls, $P < 0.001$).

3.2. The relationship between BMI and the risk of gastric high-grade dysplasia

The ORs (adjusted for age, alcohol consumption, smoking status, family history of GC or esophageal cancer, and serum total cholesterol) for gastric high-grade dysplasia based on the BMI categories for men and women are presented in Tables 3 and 4. After adjusting for age, alcohol consumption, smoking status, family history of GC or esophageal cancer, and serum total cholesterol, a BMI ranging from 27.5 to 29.9 was a risk factor for gastric high-grade dysplasia in both men and women. The adjusted ORs were 1.87 (95% CI=1.24–2.81) for men and 2.72 (95% CI=1.44–5.16) for women (BMI=27.5–29.9 vs 18.5–22.9). However, no significant associations were observed between a BMI ranging from 23.0 to 27.4 and the risk of gastric high-grade dysplasia or between the highest BMI category (30.0 or more) and the risk of gastric high-grade dysplasia in either men or women (adjusted for age, alcohol consumption, smoking status, family history of GC or esophageal cancer, and serum total cholesterol).

3.3. The relationship between BMI and the risk of gastric high-grade dysplasia stratified by the location of the tumor

As shown in Tables 5 and 6, we also examined the relationship between excess BMI and gastric high-grade dysplasia in different anatomic sites in men and women. In men, the adjusted ORs of

Table 3

Relationship between BMI and the risk of gastric high-grade dysplasia in men.

BMI, kg/m ²	Gastric high-grade dysplasia (n=537)	Control (n=546)	Univariate analysis		Multivariate analysis*	
			OR (95% CI)	P	Adjusted OR (95% CI)	P
≤18.4	17	15	1.37 (0.66–2.87)	0.401	1.10 (0.51–2.37)	0.805
18.5–22.9	114	138	1 (reference)		1 (reference)	
23.0–27.4	267	304	1.06 (0.79–1.43)	0.687	1.05 (0.78–1.43)	0.748
27.5–29.9	103	62	2.01 (1.35–3.00)	0.001	1.87 (1.24–2.81)	0.003
≥30.0	36	27	1.61 (0.92–2.82)	0.092	1.59 (0.90–2.80)	0.111

BMI = body mass index, CI = confidence interval, OR = odds ratio.

* Multivariate logistic regression model was adjusted for age, alcohol consumption, smoking status, family history of gastric cancer or esophagus cancer, and serum total cholesterol level.

Table 4

Relationship between BMI and the risk of gastric high-grade dysplasia in women.

BMI, kg/m ²	Gastric high-grade dysplasia (n=356)	Control (n=359)	Univariate analysis		Multivariate analysis*	
			OR (95% CI)	P	Adjusted OR (95% CI)	P
≤18.4	6	7	1.17 (0.39–3.58)	0.778	0.81 (0.24–2.77)	0.735
18.5–22.9	119	163	1 (reference)		1 (reference)	
23.0–27.4	157	144	1.49 (1.08–2.07)	0.016	1.37 (0.97–1.93)	0.073
27.5–29.9	44	17	3.55 (1.93–6.51)	<0.001	2.72 (1.44–5.16)	0.002
≥30.0	30	28	1.47 (0.83–2.59)	0.185	1.35 (0.74–2.46)	0.326

BMI = body mass index, CI = confidence interval, OR = odds ratio.

* Multivariate logistic regression model was adjusted for age, alcohol consumption, smoking status, family history of gastric cancer or esophagus cancer, and serum total cholesterol level.

Table 5

Relationship between BMI and the risk of gastric high-grade dysplasia stratified by the location of the tumor in men.

BMI, kg/m ²	Control (n=546)	Gastric cardia high-grade dysplasia (n=201)					Gastric noncardia high-grade dysplasia (n=336)				
		Cases	Univariate analysis		Multivariate analysis*		Cases	Univariate analysis		Multivariate analysis*	
			OR (95% CI)	P	Adjusted OR (95% CI)	P		OR (95% CI)	P	Adjusted OR (95% CI)	P
≤18.4	15	5	1.12 (0.39–3.27)	0.833	1.04 (0.35–3.04)	0.949	12	1.51 (0.67–3.40)	0.317	1.20 (0.52–2.76)	0.675
18.5–22.9	138	41	1 (reference)		1 (reference)		73	1 (reference)		1 (reference)	
23.0–27.4	304	97	1.07 (0.71–1.63)	0.737	1.01 (0.65–1.55)	0.983	170	1.06 (0.75–1.49)	0.749	1.06 (0.75–1.50)	0.739
27.5–29.9	62	38	2.06 (1.21–3.52)	0.008	1.78 (1.02–3.10)	0.042	65	0.98 (1.27–3.11)	0.003	1.98 (1.25–3.14)	0.003
≥30.0	27	20	2.49 (1.27–4.90)	0.008	2.54 (1.27–5.08)	0.008	16	1.12 (0.57–2.21)	0.744	1.03 (0.51–2.07)	0.932

BMI = body mass index, CI = confidence interval, OR = odds ratio.

* Multivariate logistic regression model was adjusted for age, alcohol consumption, smoking status, family history of gastric cancer or esophagus cancer, and serum total cholesterol level.

the BMIs ranging from 27.5 to 29.9 and those above 30.0 regarding gastric cardia high-grade dysplasia compared with the normal weight group (BMI=18.5–22.9) were 1.78 (95% CI=1.02–3.10) and 2.54 (95% CI=1.27–5.08). Similarly, the adjusted OR for BMIs ranging from 27.5 to 29.9 for gastric noncardia high-grade dysplasia was 1.98 (95% CI=1.25–3.14) in men. In contrast, no associations were observed between a BMI ranging from 23.0 to 27.4 and the risks for gastric noncardia high-

grade dysplasia or gastric cardia high-grade dysplasia in men. The highest BMI category (30.0 or more) was also not related to the risk of gastric noncardia high-grade dysplasia in men.

As in men, positive associations between increasing BMI and the risks for gastric cardia and noncardia high-grade dysplasia were observed in women. Compared with the reference group (BMI=18.5–22.9), the adjusted ORs of the BMIs ranging from 27.5 to 29.9 and those above 30.0 for women with gastric cardia

Table 6

Relationship between BMI and the risk of gastric high-grade dysplasia stratified by the location of the tumor in women.

BMI, kg/m ²	Control (n=359)	Gastric cardia high-grade dysplasia (n=152)					Gastric noncardia high-grade dysplasia (n=204)				
		Cases	Univariate analysis		Multivariate analysis*		Cases	Univariate analysis		Multivariate analysis*	
			OR (95% CI)	P	Adjusted OR (95% CI)	P		OR (95% CI)	P	Adjusted OR (95% CI)	P
≤18.4	7	3	1.71 (0.41–7.15)	0.475	1.94 (0.48–7.89)	0.357	3	0.91 (0.23–3.60)	0.890	0.46 (0.09–2.44)	0.361
18.5–22.9	163	42	1 (reference)		1 (reference)		77	1 (reference)		1 (reference)	
23.0–27.4	144	67	1.81 (1.16–2.82)	0.009	1.55 (0.97–2.49)	0.07	90	1.32 (0.91–1.93)	0.147	1.26 (0.85–1.88)	0.255
27.5–29.9	17	18	4.11 (1.95–8.65)	<0.001	2.88 (1.27–6.55)	0.012	26	3.23 (1.66–6.32)	0.001	2.88 (1.43–5.81)	0.003
≥30.0	28	22	3.05 (1.59–5.86)	0.001	2.77 (1.36–5.64)	0.005	8	0.61 (0.26–1.39)	0.236	0.70 (0.30–1.64)	0.409

BMI = body mass index, CI = confidence interval, OR = odds ratio.

* Multivariate logistic regression model was adjusted for age, alcohol consumption, smoking status, family history of gastric cancer or esophagus cancer, and serum total cholesterol level.

Table 7

Relationship between serum total cholesterol level and the risk of gastric high-grade dysplasia in men.

Cholesterol level, mmol/L	Gastric high-grade dysplasia (n=537)	Control (n=546)	Univariate analysis		Multivariate analysis*	
			OR (95% CI)	P	Adjusted OR (95% CI)	P
≤4.55	285	284	1 (reference)		1 (reference)	
>4.55	252	262	0.96 (0.76–1.22)	0.727	0.97 (0.76–1.24)	0.815

CI=confidence interval, OR=odds ratio.

*Multivariate logistic regression model was adjusted for age, alcohol consumption, smoking status, family history of gastric cancer or esophagus cancer, and body mass index.

Table 8

Relationship between serum total cholesterol level and the risk of gastric high-grade dysplasia stratified by the location of the tumor in men.

Cholesterol level, mmol/L	Control (n=546)	Gastric cardia high-grade dysplasia (n=201)				Gastric noncardia high-grade dysplasia (n=336)					
		Cases	Univariate analysis		Multivariate analysis*		Cases	Univariate analysis		Multivariate analysis*	
			OR (95% CI)	P	Adjusted OR (95% CI)	P		OR (95% CI)	P	Adjusted OR (95% CI)	P
≤4.55	284	92	1 (reference)		1 (reference)		193	1 (reference)		1 (reference)	
>4.55	262	109	1.28 (0.93–1.78)	0.131	1.28 (0.91–1.80)	0.154	143	0.80 (0.61–1.06)	0.117	0.79 (0.60–1.05)	0.106

CI=confidence interval, OR=odds ratio.

*Multivariate logistic regression model was adjusted for age, alcohol consumption, smoking status, family history of gastric cancer or esophagus cancer, and body mass index.

high-grade dysplasia were 2.88 (95% CI=1.27–6.55) and 2.77 (95% CI=1.36–5.64). A BMI ranging from 23.0 to 27.4 was not significantly related to an increased risk of gastric cardia high-grade dysplasia in women. Among the women who had gastric noncardia high-grade dysplasia, the adjusted OR of a BMI ranging from 27.5 to 29.9 was 2.88 (95% CI=1.43–5.81), whereas BMIs ranging from 23.0 to 27.4 or those above 30.0 were not independent risk factors.

3.4. The relationship between serum total cholesterol level and the risk of gastric high-grade dysplasia

In men, serum total cholesterol did not significantly vary between gastric high-grade dysplasia patients and controls (4.58±0.93 vs 4.48±0.96, P=0.083). Consequently, there were no significant associations between serum total cholesterol level and the increased risk of gastric high-grade dysplasia,

including both cardia and noncardia gastric high-grade dysplasia (Tables 7 and 8).

In contrast to men, serum total cholesterol was significantly higher in female patients than in their respective controls (4.91±0.97 vs 4.74±0.89 mmol/L, P=0.013), specifically in those with gastric noncardia high-grade dysplasia (4.92±0.98 vs 4.74±0.89 mmol/L, P=0.025) but not those with gastric cardia high-grade dysplasia (4.90±0.96 vs 4.74±0.89 mmol/L, P=0.066). In addition, high serum total cholesterol (>4.55 mmol/L) was associated with the increased risk of gastric high-grade dysplasia in women after adjusting for age, alcohol consumption, smoking status, family history of GC or esophageal cancer, and BMI. The adjusted ORs were 1.63 (95% CI=1.19–2.23) for total gastric high-grade dysplasia (Table 9) and 1.83 (95% CI=1.25–2.69) for gastric noncardia high-grade dysplasia (Table 10). However, higher serum total cholesterol was not a substantial risk factor for gastric cardia high-grade

Table 9

Relationship between serum total cholesterol level and the risk of gastric high-grade dysplasia in women.

Cholesterol level, mmol/L	Gastric high-grade dysplasia (n=356)	Control (n=359)	Univariate analysis		Multivariate analysis*	
			OR (95% CI)	P	Adjusted OR (95% CI)	P
≤4.55	123	164	1 (reference)		1 (reference)	
>4.55	233	195	1.59 (1.18–2.15)	0.002	1.63 (1.19–2.23)	0.003

CI=confidence interval, OR=odds ratio.

*Multivariate logistic regression model was adjusted for age, alcohol consumption, smoking status, family history of gastric cancer or esophagus cancer, and body mass index.

Table 10

Relationship between serum total cholesterol level and the risk of gastric high-grade dysplasia stratified by the location of the tumor in women.

Cholesterol level, mmol/L	Control (n=359)	Gastric cardia high-grade dysplasia (n=152)				Gastric noncardia high-grade dysplasia (n=204)					
		Cases	Univariate analysis		Multivariate analysis*		Cases	Univariate analysis		Multivariate analysis*	
			OR (95% CI)	P	Adjusted OR (95% CI)	P		OR (95% CI)	P	Adjusted OR (95% CI)	P
≤4.55	164	56	1 (reference)		1 (reference)		67	1 (reference)		1 (reference)	
>4.55	195	96	1.44 (0.98–2.13)	0.066	1.34 (0.88–2.03)	0.169	137	1.71 (1.18–2.46)	0.004	1.83 (1.25–2.69)	0.002

CI=confidence interval, OR=odds ratio.

*Multivariate logistic regression model was adjusted for age, alcohol consumption, smoking status, family history of gastric cancer or esophagus cancer, and body mass index.

dysplasia in women (adjusted OR = 1.34, 95% CI = 0.88–2.03; Table 10).

4. Discussion

This case-control study consistently demonstrated that a BMI ranging from 27.5 to 29.9 was an independent risk factor for gastric high-grade dysplasia in both men and women. Concurrently, the 2 highest BMI categories (27.5–29.9 and 30.0 or more) were positively associated with an increased risk of gastric cardia high-grade dysplasia in both men and women; only a BMI ranging from 27.5 to 29.9 increased the risk of gastric noncardia high-grade dysplasia in both men and women. In addition, we observed that a higher serum total cholesterol level was related to an increased risk of gastric noncardia high-grade dysplasia in women. In contrast, our study did not find an association between serum total cholesterol and gastric cardia high-grade dysplasia in either men or women. The role of serum total cholesterol in gastric cardia high-grade dysplasia requires additional investigation. Old age, alcohol use, cigarette smoking, and family history of GC were proved to be indisputable risk factors for GC. To avoid attenuating the relationships among BMI category, serum total cholesterol level, and the risk of gastric high-grade dysplasia, multivariate logistic regression models were performed to adjust for these potential confounders.

Obesity has been reported to be associated with an increased risk of many types of cancer. Several prospective and retrospective studies have provided support for the hypothesis that higher BMIs in patients are positively associated with a higher incidence of cardiac GC.^[17,36,39–44] In contrast, no significant link was found between obesity and an increased risk for noncardiac GC. The mechanisms that underlie obesity-induced GC are under investigation. Gastroesophageal reflux has been commonly accepted as a potential mechanism underlying the relationship between obesity and cardiac GC.^[45] In addition, obese patients often have a high level of insulin-like growth factor 1, which has been associated with the development of many types of cancers including GC.^[46] In addition, the accumulation of adipose tissue induces imbalances of adiponectin and leptin, which are related to an increased risk for GC.^[47–49] Concurrently, obesity is associated with low-grade systemic inflammation, and recent studies have suggested that common inflammatory cytokines such as IL-6, IL-17, TNF α , and MCP-1 can either induce the growth or suppress the apoptosis of human GC cell lines.^[50–53]

Previous studies performed in Western countries categorized BMI using the following guidelines proposed by the WHO: <18.5 kg/m² (underweight), 18.5 to 24.9 kg/m² (normal weight), 25 to 29.9 kg/m² (overweight), 30 to 34.9 kg/m² (obese class I), 35 to 39.9 kg/m² (obese class II), and 40 kg/m² and above (obese class III).^[37] In certain Asian populations, specific BMIs reflect higher percentages of body fat than they do in White European populations. The proportion of Asians with risk factors for cardiovascular disease and type 2 diabetes was substantial below the current WHO BMI cut-off point of 25 kg/m². Consequently, the present WHO BMI cut-off does not provide a sufficient basis for taking action on the risks related to overweight and obesity in many Asian populations.^[37] In the present analysis, the BMI categories for overweight and obesity were changed to 23.0 to 27.4 kg/m² (overweight), 27.5 to 29.9 kg/m² (obesity), and 30.0 kg/m² and above (severe obesity). The BMI cut-off point of ≥ 27.5 kg/m² was used as a cut-off point for obesity.

Relationships between serum total cholesterol and several types of cancer have been observed in modern research. These

results suggest a positive association between high serum total cholesterol and an increased risk for rectal cancer.^[54] Among smokers, high serum total cholesterol was related to an increased risk of advanced prostate cancer, but high serum high-density lipoprotein (HDL) cholesterol reduced the risk of prostate cancer overall.^[55] In contrast, inverse relationships have been found between serum total cholesterol and cancers of the pancreas, liver, intrahepatic bile duct, hematopoietic tissue, and skin (nonmelanoma) among men as well as between serum total cholesterol and cancers of the breast, gallbladder, hematopoietic tissue, and skin (melanoma) among women.^[56,57] With regard to gastric malignancy, Tornberg et al^[58] found that low serum cholesterol was a risk factor for developing GC. Asano et al^[35] observed a similar result, especially with regard to intestinal-type GC. On the contrary, Wulaningsih et al^[54] observed a positive association between higher apolipoprotein B/apolipoprotein A-I ratio and the risk of GC. However, no significant association between serum cholesterol levels and GC was found in a Finnish cohort study.^[59] The large European cohort, Me-Can, also reported no association between triglycerides and GC risk.^[60] Several mechanisms have been hypothesized to explain the relationship between total cholesterol and cancer risk. Hypercholesterolemia has been related to increased inflammatory activity, which might be conducive to cancer development.^[61] Furthermore, several pathways that play important roles in tumorigenesis, such as the Akt and sonic hedgehog signaling pathways, are cholesterol sensitive. Thus, higher cholesterol levels might induce their pro-carcinogenic activities.

The clinical significance of gastric dysplasia, especially that of gastric high-grade dysplasia, as a direct precursor lesion of GC has been stressed recently. Gastric high-grade dysplasia has progressed to GC in a high percentage of cases (74%),^[62] and some lesions with gastric high-grade dysplasia have been associated with submucosal invasion.^[63] Consequently, gastric high-grade dysplasia might be considered as a histological marker for gastric carcinoma. However, data were scarce concerning the relationship between obesity and the risk of gastric high-grade dysplasia or the relationship between serum total cholesterol level and the risk of gastric high-grade dysplasia. Kim et al^[32] indicated that obesity was related to an increased risk of gastric dysplasia in women. In contrast, 2 other Korean case-control studies indicated no significant association between obesity and gastric dysplasia,^[64,65] which was inconsistent with our findings. However, these studies enrolled fewer patients than did the present study, and the previous studies did not focus exclusively on gastric high-grade dysplasia.

In the present study, female patients with higher BMIs showed higher serum total cholesterol levels (Tables S1 and S2, <http://links.lww.com/MD/B231>). The increase in serum total cholesterol level might be an effect of high BMIs. However, elevated serum total cholesterol was identified as an independent risk factor for gastric noncardia high-grade dysplasia regardless of BMI classification using a multivariate logistic regression model. This observational study cannot establish cause and effect. Several studies have suggested that dyslipidemia might enhance oxidative stress and chronic inflammation, which are highly related to mechanisms linked to carcinogenesis including gastrointestinal malignancy.^[66,67] Higher serum total cholesterol was proved to increase the risk of gastric noncardia high-grade dysplasia only in women not man in the present study, which might be attributed to the more smokers and drinkers in male controls compared with female controls. Cigarette smoking and alcohol consumption were associated with high serum non-HDL

cholesterol level,^[68] which might attenuate the difference of serum total cholesterol between male gastric noncardia high-grade dysplasia patients and controls. The present analysis extended the findings of previous analyses of the association between serum total cholesterol and the risk of gastric dysplasia. Kim identified higher total cholesterol as an independent risk factor for gastric dysplasia with an OR of 6.299 (95% CI=1.277–31.076),^[64] which was consistent with the present study. However, total cholesterol was not associated with an increased risk of gastric dysplasia in the study conducted by Jung; however, gastric dysplasia risk significantly increased among individuals with higher low-density lipoprotein levels.^[65] Differences in diet related to GC risk might explain these conflicting findings.

To the best of our knowledge, this study was the first to assess the relationships among BMI, serum total cholesterol level, and the risk of gastric high-grade dysplasia. However, several limitations were present regarding this analysis. First, observational studies cannot establish causal relationships because other associated factors might serve as confounders. Nevertheless, if the main risk for gastric high-grade dysplasia was a higher BMI (which successively increased the risk of GC), then we might expect gastric high-grade dysplasia to lead to weight reduction. Under this scenario, the association between obesity and gastric high-grade dysplasia would become weaker. *Helicobacter pylori* infection was a well-established risk factor for GC.^[69] However, *H pylori* status as well as environmental, occupational, and dietary exposures were not available for all of the patients or controls. In particular, *H pylori* status was available for few controls. Consequently, the present study did not exclude confounding because of unmeasured factors (e.g., *H pylori* infection status, physical activity, and differences in diet and ethnicities). A similar limitation existed for the analyses of serum total cholesterol and gastric high-grade dysplasia risk. Second, we used self-reported body weight and height to calculate the BMIs of the participants who lost weight over the last 3 years. Although self-reported body weight and height are highly consistent with measured body weight and height,^[70] the small error that exists is generally systematic, with an overestimation of height and an underestimation of weight, especially at higher weights.^[71] Consequently, our measure of BMI most likely underestimated the true BMIs of the participants who lost weight over the last 3 years. In addition, we had no direct measure of lean body mass or central adiposity (e.g., abdominal circumference or waist-to-hip ratio). Third, the present study found that a BMI of 30.0 or more was not an independent risk factor for gastric noncardia high-grade dysplasia in either men or women; the small number of patients with BMIs of 30.0 or more might account for this result. Fourth, serum total cholesterol was determined at a single time point, which might lead to the misclassification of a participant's usual cholesterol level because of intraindividual variation in serum total cholesterol over the long term. Such a misclassification had a tendency to attenuate the observed association.^[35] In addition, BMIs were also measured at a single point, although BMI does not typically decrease with age. We collected the usual data for body weight and height before weight loss for participants who lost weight within 3 years, but we were unable to evaluate long-term patterns of BMI.

In summary, the present study suggests that increased BMI is a risk factor for the development of gastric high-grade dysplasia, especially gastric cardia high-grade dysplasia, in both men and women. Concurrently, high serum total cholesterol was related to an increased risk of gastric noncardia high-grade dysplasia in women. Given the limitations of the present study, large-scale and

well-designed cohort studies should be conducted to investigate the relationships among obesity, serum total cholesterol level, and the risk of gastric high-grade dysplasia in different populations.

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