Relationship between body mass index and the risk of early gastric cancer and dysplasia regardless of *Helicobacter pylori* infection

Hee Jin Kim · Nayoung Kim · Hyun Young Kim · Hye Seung Lee ·
Hyuk Yoon · Cheol Min Shin · Young Soo Park · Do Joong Park ·
Hyung Ho Kim · Kyoung-Ho Lee · Young-Hoon Kim · Hee Man Kim ·
Dong Ho Lee

Received: 14 March 2014 / Accepted: 30 August 2014 / Published online: 21 September 2014
© The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2014

Abstracts

Background Obesity is known to be associated with an increased risk of gastric cardia cancer but not with non-cardia cancer. In terms of gastric dysplasia, few studies have evaluated its relationship with obesity. In addition, no study on the relationship between obesity and the risk of gastric cancer has analyzed the status of *Helicobacter pylori* infection.

Methods A case–control study was designed to investigate the relationship between obesity and the risk of gastric cancer and dysplasia adjusted for the status of *H. pylori* infection in Koreans. Nine hundred ninety-eight gastric

cancer patients, 313 gastric dysplasia patients, and 1,288 subjects with normal endoscopic findings were included.

Results As gender differences could be the largest confounding factor, the risk of gastric cancer and dysplasia with an increasing body mass index (BMI) was analyzed in men and women, separately, and was adjusted for age, smoking, drinking, family history of gastric cancer, *H. pylori* infection, atrophic gastritis, intestinal metaplasia, and serum pepsinogen I/pepsinogen II ratio. Obesity (BMI 25 kg/m² or greater but less than 30 kg/m²) was associated with increased risk of early gastric cancer [adjusted odds ratio (aOR) 1.657; 95 % confidence interval (CI) 1.086–2.528; *P* = 0.019] and well or moderately differentiated adenocarcinoma (aOR 1.566; 95 % CI 1.011–2.424; *P* = 0.044) compared with normal BMI status (BMI < 23 kg/m²) in men. Obesity was related to gastric dysplasia (aOR 2.086; 95 % CI 1.011–4.302; *P* = 0.047) in women.

Conclusions The effect of obesity on gastric cancer showed a gender difference. That is, in men it was related to increased risk of early gastric cancer and well or moderately differentiated adenocarcinoma, but it was associated with gastric dysplasia in women regardless of *H. pylori* infection in Korea. Further research into this difference is necessary.

Keywords Body mass index · Gastric cancer · Gastric dysplasia · *Helicobacter pylori*

H. J. Kim · N. Kim (✉) · H. Y. Kim · H. Yoon ·
C. M. Shin · Y. S. Park · D. H. Lee
Department of Internal Medicine, Seoul National University
Bundang Hospital, 173-82 Gumi-ro, Bundang-gu, Seongnam,
Gyeonggi-do 463-707, South Korea
e-mail: nayoungkim49@empal.com

N. Kim · D. H. Lee
Department of Internal Medicine and Liver Research Institute,
Seoul National University College of Medicine,
Seoul, South Korea

H. S. Lee
Department of Pathology, Seoul National University Bundang
Hospital, Seongnam, Gyeonggi-do, South Korea

D. J. Park · H. H. Kim
Department of Surgery, Seoul National University Bundang
Hospital, Seongnam, Gyeonggi-do, South Korea

K.-H. Lee · Y.-H. Kim
Department of Radiology, Seoul National University Bundang
Hospital, Seongnam, Gyeonggi-do, South Korea

H. M. Kim
Department of Internal Medicine, Yonsei University Wonju
College of Medicine, Wonju, South Korea

Introduction

Despite the decreasing incidence of gastric cancer in recent decades worldwide, it remains the fourth commonest cancer in the world and the third-leading cause

of cancer-related death in men and the fifth-leading cause of cancer-related death in women [1]. Gastric cancer is classified as gastric noncardia cancer and cardia cancer depending on the anatomical location of the lesion, and these two types of gastric cancer have distinct epidemiologic and clinical characteristics. The incidence of gastric noncardia cancer has gradually declined as a result of changing lifestyles, whereas that of cardia cancer has increased sharply in Western countries [2, 3]. There is evidence of an increased risk of gastric noncardia cancer related to chronic *Helicobacter pylori* infection [4], tobacco smoking [5], alcohol abuse [6], salty and smoked food [7], and low consumption of fresh fruits and vegetables [8]. By contrast, gastric cardia cancer may be related to gastroesophageal reflux [9], white race [10], male gender [10], and tobacco smoking [11]. *H. pylori* infection has been verified to be a key factor in gastric noncardia cancer, whereas the role of *H. pylori* infection in gastric cardia cancer remains controversial [12].

Obesity has increased steadily worldwide. There is sufficient evidence of a positive relationship between obesity and the risk of colon cancer, postmenopausal breast cancer, endometrial cancer, renal cell cancer, and adenocarcinoma of the esophagus [13]. On the other hand, previous studies have shown mixed results with regard to the relationship between obesity and gastric cancer. Recently, several meta-analyses have found that overweight and obese individuals are more likely to be at risk of gastric cardia cancer but not of noncardia cancer [14, 15]. However, no study has explored the effect of *H. pylori* infection on the relationship between obesity and the risk of gastric cancer, which may be an important confounder. In addition, stages of gastric cancer, including early and advanced stages, have yet to be clearly identified.

Gastric dysplasia is considered a premalignant lesion of intestinal-type gastric cancer, and *H. pylori* is known to cause gastric cancer progressively from atrophic gastritis to intestinal metaplasia, dysplasia, and finally cancer [4]. Unlike in the case of colorectal adenomas, for which obesity is associated with an increased risk [16], few studies have explored the relationship between obesity and the risk of gastric dysplasia [17].

Given the above background, the present study aimed to determine whether obesity, as measured by the body mass index (BMI), is related to gastric cancer and dysplasia after adjustment for *H. pylori* infection and other confounding factors in men and women. In addition, the study examines whether obesity is related to various subgroups of gastric cancer stratified by the location, stage, and histologic subtype of the tumor.

Materials and methods

Study subjects

This study was designed as a single-center case-control study. Patients histologically diagnosed with gastric cancer or dysplasia were prospectively enrolled at Seoul National University Bundang Hospital between June 2003 and August 2013. All participants were ethnically Korean, and most had undergone standard endoscopy as part of a screening program for premalignant gastric mucosal lesions or gastric cancer. All patients with gastric cancer or dysplasia were histologically confirmed by the surgical or endoscopic submucosal dissection specimen. However, for subjects who could not undergo surgery or endoscopic submucosal dissection because of metastasis or patient comorbidity, a diagnosis of gastric cancer was made with endoscopic biopsy. Patients who had another underlying type of cancer and a history of gastric resection were excluded from this study. In this study, gastric cancer is defined as gastric carcinomas including well, moderately, and poorly differentiated tubular adenocarcinomas, papillary adenocarcinomas, mucinous adenocarcinomas, signet ring cell carcinomas, and undifferentiated carcinomas. Those subjects who underwent endoscopy for screening or complained of mild dyspepsia and agreed to receive four types of *H. pylori* studies in advance in the same study period but did not show any evidence of gastric cancer or dysplasia, mucosa-associated lymphoid tissue lymphoma, or esophageal cancer were assigned to control groups. All patients and controls received endoscopy from N.K. Each participant completed an informed consent form and a questionnaire about his or her family history of having first-degree relatives with gastric cancer, smoking and alcohol consumption habits, and history of *H. pylori* eradication under the supervision of a well-trained interviewer before endoscopy. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital on January 29, 2014 (Institutional Review Board number B-1401/234-110).

Determination of the *H. pylori* infection status

For the determination of the *H. pylori* infection status, ten biopsy specimens were taken from the gastric mucosa of each patient (two biopsy specimens from each of the greater curvature of the antrum and body and three specimens from each of the lesser curvature of the antrum and body) during upper endoscopy. Among these ten specimens, four were used for the histologic evaluation of *H. pylori* infection by modified Giemsa staining [18]. Another four specimens from the four gastric mucosa areas

mentioned earlier were used for *H. pylori* culturing. The remaining two specimens from the lesser curvature of the antrum and body were analyzed with a rapid urease test (CLOtest; Delta West, Bentley, Australia). All biopsy specimens were examined by an experienced pathologist (H.S.L.) who was unaware of patient details. Immunoglobulin G specific for *H. pylori* was screened by an enzyme-linked immunosorbent assay in each subject's serum (Genedia *H. pylori* enzyme-linked immunosorbent assay; Green Cross Medical Science, Eumsung, South Korea), and the Korean strain was used as an antigen in this *H. pylori* antibody test [19]. If the result of at least one of these four tests (histologic evaluation, rapid urease test, culturing, *H. pylori* serologic test) was positive or the patient had a history of *H. pylori* eradication, the patient was determined as positive for *H. pylori* infection. The patients with all negative results from these four tests and no history of *H. pylori* eradication were diagnosed as negative for *H. pylori* infection.

Evaluation of gastric atrophy and intestinal metaplasia

To evaluate gastric atrophy by the serum pepsinogen test, a fasting serum sample was collected from patients, and serum concentrations of pepsinogen I and pepsinogen II were measured using the latex-enhanced turbidimetric immunoassay (Shima Laboratories, Tokyo, Japan). A pepsinogen I/pepsinogen II ratio less than 3.0 is generally accepted as indicating atrophy [20].

To evaluate further the severity of gastric atrophy and intestinal metaplasia, updated Sydney system scores were applied to the four biopsy specimens after the hematoxylin and eosin stain.

Clinicopathologic characteristics

Baseline characteristics of subjects, including their age, gender, smoking status, drinking status, first-degree familial history of gastric cancer, and BMI, were assessed. Their height and weight were checked or measured at the time of endoscopy in the endoscopy room, and the BMI was computed as weight in kilograms per square surface area in square meters (kg/m^2). According to the International Obesity Task Force criteria for the Asia-Pacific population, BMI scores were classified as follows: normal (below 23 kg/m^2), overweight (23 kg/m^2 or greater but below 25 kg/m^2), obese (25 kg/m^2 or greater but below 30 kg/m^2), and severe obesity (30 kg/m^2 or greater) [21].

Surgical specimens of patients with gastric cancer were evaluated according to gross and histologic features and the tumor location by a pathologist (H.S.L.) based on the seventh edition of the American Joint Committee on Cancer staging manual. Early gastric carcinomas (EGCs) were

defined as invasive carcinomas confined to the mucosa and/or submucosa with or without lymph node metastases regardless of tumor size. Advanced gastric carcinomas (AGCs) were defined as carcinomas invading the muscularis propria or beyond. In the case of patients with no surgery, multiple modalities including endoscopy, endoscopic ultrasonography, and computed tomography were synthesized to determine the tumor location. Gastric cardia cancer was defined as cancer located within 2 cm below the gastroesophageal junction. Tumors arising in the distal part of this area were defined as gastric noncardia cancer. Histologic type was classified into differentiated type (well-differentiated or moderately differentiated adenocarcinoma) or undifferentiated type (poorly differentiated adenocarcinoma or signet ring cell carcinoma) according to Japanese guideline [22].

Statistical analysis

Categorical variables were analyzed by a chi square test, and continuous variables were analyzed by Student's *t* test. The effects of BMI on the risk of gastric cancer and dysplasia were represented as odds ratios (ORs) with the 95 % confidence interval (CI) by logistic regression in men and women. In multivariate analyses, all risk estimates were adjusted for the following potential confounding factors: age (in years), smoking status, drinking status, family history of gastric cancer, atrophic gastritis by histologic evaluation, intestinal metaplasia by histologic evaluation, and the pepsinogen I/pepsinogen II ratio. Statistical significance was set to 0.05, and all statistical analyses were conducted using PASW Statistics version 20.0 (IBM, Armonk, NY, USA).

Results

Characteristics of subjects

In this study, 998 patients with gastric cancer (663 males and 335 females) and 313 patients with gastric dysplasia (214 males and 99 females) were enrolled during the study period, and 1,288 subjects (628 males and 660 females) were included as control subjects. The gender-specific baseline characteristics of the patients with gastric cancer and dysplasia and the controls are presented in Tables 1 and 2. The males and females with gastric cancer and dysplasia were older, had higher incidence of *H. pylori* infection, more histologic atrophy and intestinal metaplasia, and lower mean serum pepsinogen I/pepsinogen II ratio than the controls. There were more current/ex-smokers in the patients with gastric cancer than in the controls for the males. The females with gastric cancer

were more likely than the controls to have a first-degree family history of gastric cancer, be a current/ex-smoker, and a drinker. In males, there was a statistically significant difference between the mean BMI of patients with gastric cancer and that of the controls ($23.27 \pm 2.98 \text{ kg/m}^2$ for

gastric cancer patients vs $23.63 \pm 2.99 \text{ kg/m}^2$ for controls, $P = 0.028$). In females, the mean BMI of patients with gastric dysplasia was significantly higher than that of controls ($24.17 \pm 3.47 \text{ kg/m}^2$ for gastric dysplasia patients vs $22.62 \pm 3.14 \text{ kg/m}^2$ for controls, $P < 0.001$).

Table 1 Characteristics of case patients and controls for males

	Controls (<i>n</i> = 628)	Gastric cancer patients (<i>n</i> = 663)	Gastric dysplasia patients (<i>n</i> = 214)	<i>P</i> (controls vs. gastric cancer patients)	<i>P</i> (controls vs. gastric dysplasia patients)
Age (years, mean $\pm$ SD)	53.81 $\pm$ 14.12	61.01 $\pm$ 11.14	62.43 $\pm$ 10.16	<0.001	<0.001
Age categories				<0.001 ^b	<0.001 ^b
<30	29 (4.6)	5 (0.8)	0 (0.0)		
30–39	85 (13.5)	15 (2.3)	4 (1.9)		
40–49	123 (19.6)	90 (13.6)	18 (8.4)		
50–59	155 (24.7)	162 (24.4)	63 (29.4)		
60–69	152 (24.2)	231 (34.8)	74 (34.6)		
70–79	68 (10.8)	141 (21.3)	49 (22.9)		
≥ 80	16 (2.5)	19 (2.9)	6 (2.8)		
Height (cm, mean $\pm$ SD)	169.95 $\pm$ 6.35	167.70 $\pm$ 5.93	167.15 $\pm$ 6.03	<0.001	<0.001
Weight (kg, mean $\pm$ SD)	68.37 $\pm$ 10.16	65.58 $\pm$ 9.98	66.22 $\pm$ 8.58	<0.001	0.003
BMI (kg/m^2 , mean $\pm$ SD)	23.63 $\pm$ 2.99	23.27 $\pm$ 2.98	23.67 $\pm$ 2.60	0.028	0.849
Smoking status ^a				0.019	0.112
Nonsmoker	121 (19.3)	95 (14.4)	31 (14.5)		
Current/ex-smoker	505 (80.7)	564 (85.6)	183 (85.5)		
Drinking status ^a				0.383	0.088
Never/rare drinker	371 (59.7)	410 (62.1)	113 (53.1)		
Drinker	250 (40.3)	250 (37.9)	100 (46.9)		
Family history of gastric cancer ^a				0.197	0.667
No	478 (77.0)	526 (79.9)	167 (78.4)		
Yes	143 (23.0)	132 (20.1)	46 (21.6)		
<i>Helicobacter pylori</i> status				<0.001	<0.001
Negative	144 (22.9)	91 (13.7)	25 (11.7)		
Positive	484 (77.1)	572 (86.3)	189 (88.3)		
PG I (ng/ml, mean $\pm$ SD) ^a	4.36 $\pm$ 3.45	3.77 $\pm$ 2.79	5.48 $\pm$ 20.73	0.001	0.443
PG II (ng/ml, mean $\pm$ SD) ^a	23.38 $\pm$ 25.98	23.46 $\pm$ 25.72	17.61 $\pm$ 16.67	0.958	<0.001
PG I/PG II ratio ^a	4.36 $\pm$ 3.93	3.18 $\pm$ 2.28	3.01 $\pm$ 1.67	<0.001	<0.001
≤ 3	158 (28.1)	355 (55.6)	120 (58.8)		
>3	405 (71.9)	284 (44.4)	84 (41.2)		
AG, histologic evaluation in either antrum or body ^a				<0.001	<0.001
Absent	263 (54.8)	137 (24.8)	31 (19.0)		
Present	217 (45.2)	416 (75.2)	132 (81.0)		
IM, histologic evaluation in either antrum or body ^a				<0.001	<0.001
Absent	398 (63.9)	134 (20.3)	30 (14.1)		
Present	225 (36.1)	526 (79.7)	183 (85.9)		

The data in *parentheses* are percentages. Numbers in *italic type* indicate statistical significance

SD standard deviation, PG pepsinogen, AG atrophic gastritis, IM intestinal metaplasia, BMI body mass index

^a Some data are missing, and missing values are not included

^b *P* for trends

Table 3 presents the pathologic characteristics of patients with gastric cancer according to gross tumor classification in each gender. There were 393 male EGC patients and 270 male AGC patients. Nineteen male EGC patients (4.8 %) and 35 male AGC patients (13 %) had

cancer localized to the cardia. More than half of the male patients with EGC had differentiated-type gastric cancer, and more than half of the male patients with AGC had undifferentiated-type gastric cancer. There were 203 female EGC patients and 132 female AGC patients. Two

Table 2 Characteristics of case patients and controls for females

	Controls (<i>n</i> = 660)	Gastric cancer patients (<i>n</i> = 335)	Gastric dysplasia patients (<i>n</i> = 99)	<i>P</i> (controls vs gastric cancer patients)	<i>P</i> (controls vs gastric dysplasia patients)
Age (years, mean ± SD)	53.96 ± 12.50	58.04 ± 13.82	64.31 ± 8.16	<0.001	<0.001
Age categories				<0.001 ^b	<0.001 ^b
<30	13 (2.0)	3 (0.9)	0 (0.0)		
30–39	78 (11.8)	37 (11.0)	0 (1.9)		
40–49	153 (23.2)	58 (17.3)	4 (4.0)		
50–59	178 (27.0)	72 (21.5)	21 (21.2)		
60–69	175 (26.5)	90 (26.9)	41 (41.4)		
70–79	54 (8.2)	60 (17.9)	32 (32.3)		
≥80	9 (1.4)	15 (4.5)	1 (1.0)		
Height (cm, mean ± SD)	158.07 ± 5.50	156.04 ± 6.27	153.62 ± 6.39	<0.001	<0.001
Weight (kg, mean ± SD)	56.52 ± 8.08	55.97 ± 8.85	56.99 ± 8.29	0.326	0.590
BMI (kg/m ² , mean ± SD)	22.62 ± 3.14	23.00 ± 3.48	24.17 ± 3.47	0.084	<0.001
Smoking status ^a				0.022	0.872
Nonsmoker	595 (91.4)	287 (86.7)	90 (90.9)		
Current/ex-smoker	56 (8.6)	44 (13.3)	9 (9.1)		
Drinking status ^a				0.017	0.635
Never/rare drinker	607 (93.5)	296 (89.2)	91 (94.8)		
Drinker	42 (6.5)	36 (10.8)	5 (5.2)		
Family history of gastric cancer ^a				0.006	0.914
No	460 (70.2)	259 (78.5)	69 (69.7)		
Yes	195 (29.8)	71 (21.5)	30 (30.3)		
<i>Helicobacter pylori</i> status				<0.001	<0.001
Negative	191 (28.9)	43 (12.8)	10 (10.1)		
Positive	469 (71.1)	292 (87.2)	89 (89.9)		
PG I (ng/ml, mean ± SD) ^a	4.18 ± 2.16	4.24 ± 2.50	4.66 ± 5.63	0.720	0.417
PG II (ng/ml, mean ± SD) ^a	21.93 ± 21.77	24.26 ± 24.91	20.16 ± 13.70	0.146	0.295
PG I/PG II ratio ^a	3.73 ± 2.26	3.31 ± 1.74	2.78 ± 1.42	0.002	<0.001
≤3	257 (45.1)	168 (52.8)	64 (68.1)		
>3	313 (54.9)	150 (47.2)	30 (31.9)		
AG, histologic evaluation in either antrum or body ^a				<0.001	<0.001
Absent	360 (66.8)	94 (36.2)	17 (23.0)		
Present	179 (33.2)	166 (63.8)	57 (77.0)		
IM, histologic evaluation in either antrum or body ^a				<0.001	<0.001
Absent	484 (73.9)	127 (38.3)	18 (18.4)		
Present	171 (26.1)	205 (61.7)	80 (81.6)		

The data in *parentheses* are percentages. Numbers in *italic type* indicate statistical significance

SD standard deviation, PG pepsinogen, AG atrophic gastritis, IM intestinal metaplasia, BMI body mass index

^a Some data are missing, and missing values are not included

^b *P* for trends

(1 %) of the female patients with EGC and 11 (8.3 %) of the female patients with AGC had cancer located in the cardia. Signet ring cell carcinoma was most frequently reported in female patients with EGC (31 %).

Relationship between obesity and the risk of gastric cancer and dysplasia

Table 4 shows the distribution of patients with gastric cancer and dysplasia and controls according to the BMI categories in males and females. After adjusting for age, smoking status, drinking status, first-degree family history of gastric cancer, *H. pylori* infection, histologic atrophic gastritis and intestinal metaplasia, and serum pepsinogen I/pepsinogen II ratio, we observed BMI was not statistically significantly associated with the risk of gastric cancer and gastric dysplasia in males. Likewise, there was no significant association between BMI and the risk of gastric cancer in females. However, obesity (BMI 25 kg/m² or greater but below 30 kg/m²) was significantly associated with an increased risk of gastric dysplasia compared with normal BMI status (BMI < 23 kg/m²) in females [adjusted OR (aOR) 2.086; 95 % CI 1.011–4.302;

$P = 0.047$], whereas there was no significant association between severe obesity (BMI ≥ 30 kg/m²) and the risk of gastric dysplasia (aOR 2.713; 95 % CI 0.791–9.306; $P = 0.112$).

Relationship between obesity and the risk of gastric cancer stratified by the gross classification, location, and histologic type of the tumor

The association between BMI and the risk of gastric cancer stratified by the gross tumor classification, location, and histologic type were examined in males (Table 5) and females (Table 6). Obesity (BMI 25 kg/m² or greater but below 30 kg/m²) was statistically significantly related to the increased risk of EGC (aOR 1.657; 95 % CI 1.086–2.528, $P = 0.019$) and differentiated-type gastric cancer (aOR 1.566; 95 % CI 1.011–2.424, $P = 0.044$) compared with normal BMI status (BMI < 23 kg/m²) in males. No associations were seen between obesity and the risks of AGC, gastric noncardia cancer, cardia cancer, and undifferentiated-type gastric cancer in males. Severe obesity (BMI ≥ 30 kg/m²) was not significantly associated with the risk of any subgroup of gastric cancer in males.

Table 3 Pathologic characteristics of patients with gastric cancer according to gross tumor stage in males and females

	Males		Females	
	Early gastric cancer (<i>n</i> = 393)	Advanced gastric cancer (<i>n</i> = 270)	Early gastric cancer (<i>n</i> = 203)	Advanced gastric cancer (<i>n</i> = 132)
Tumor location (%) ^a				
Noncardia	371 (94.4)	222 (82.2)	201 (99.0)	118 (89.4)
Cardia	19 (4.8)	35 (13.0)	2 (1.0)	11 (8.3)
Mixed	3 (0.8)	13 (4.8)	0 (0.0)	3 (2.3)
Lauren histotype (%)				
Intestinal	297 (75.6)	122 (45.2)	103 (50.7)	33 (25.0)
Diffuse	84 (21.4)	134 (49.6)	94 (46.3)	94 (71.2)
Mixed	8 (2.0)	8 (3.0)	5 (2.5)	4 (3.0)
Unidentified	4 (1.0)	6 (2.2)	1 (0.5)	1 (0.8)
Histologic type (%)				
Tubular ADC, W/D	162 (41.2)	7 (2.6)	48 (23.6)	4 (3.0)
Tubular ADC, M/D	129 (32.8)	106 (39.3)	52 (25.6)	28 (21.2)
Tubular ADC, P/D	56 (14.2)	113 (41.9)	37 (18.2)	71 (53.8)
Signet ring cell carcinoma	41 (10.4)	29 (10.7)	63 (31.0)	26 (19.7)
Mucinous ADC	3 (0.8)	9 (3.3)	1 (0.5)	3 (2.3)
Papillary ADC	2 (0.5)	4 (1.5)	2 (1.0)	0 (0.0)
Undifferentiated carcinoma	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)

The data in *parentheses* are percentages

ADC adenocarcinoma, W/D well differentiated, M/D moderately differentiated, P/D poorly differentiated

^a Gastric cardia cancer is defined as a type of cancer located within 2 cm below the gastroesophageal junction. Tumors arising in the distal part of this area are defined as gastric noncardia cancer. Mixed cancer includes both gastric cardia cancer and noncardia cancer

In females, there were no statistically significant associations between BMI and any subgroup of gastric cancer (Table 6)

Discussion

In this case-control study, the relationships between BMI and the risk of gastric cancer and dysplasia were investigated by considering the *H. pylori* infection status and other confounding factors in males and females. We observed that there were no significant relationships between obesity and the risk of gastric cancer or dysplasia in males. However, we found that obesity was related to an increased risk of EGC and well or moderately differentiated adenocarcinoma regardless of *H. pylori* infection in males, with the exception in males with BMI ≥ 30 kg/m². Although obesity was not related to an increased risk of gastric cancer or any subgroup of gastric cancer, a positive association between obesity and the risk of gastric dysplasia was seen in females, with the exception of females with BMI ≥ 30 kg/m².

Previous case-control and cohort studies have shown the tendency of higher BMIs in patients with gastric cardia cancer. Several potential mechanisms have been proposed as underlying the relationship between an increased BMI and the risk of gastric cardia cancer. Obesity promotes gastroesophageal reflux by increasing intra-abdominal

pressure [23], which predisposes to Barrett's esophagus and thus to adenocarcinoma of the gastroesophageal junction [24]. Other mechanisms may also be involved, given that some studies have demonstrated a relationship between obesity and gastric cardia cancer regardless of gastroesophageal reflux [25]. The accumulation of adipose tissue induces multiple molecular changes such as hyperinsulinemia, elevated levels of insulin-like growth factors, adipokine imbalance, and increased estrogen levels, which can increase cell proliferation and impair apoptosis and consequently preneoplastic and neoplastic cell growth [26]. In addition, obesity has been recognized as a proinflammatory state leading to elevated levels of proinflammatory cytokines such as tumor necrosis factors and interleukin-6 [27]. By contrast, most previous studies have shown no relationship between obesity and gastric noncardia cancer. People at higher risk of gastric noncardia cancer are often heavy smokers and heavy drinkers, and thus are often malnourished. Further, a negative relationship between BMI and *H. pylori* infection is likely to be from another mechanism. *H. pylori* is suspected to be a cause of growth retardation during childhood [28]. *H. pylori*-related gastritis may have a direct effect on the reduction of food intake and impaired nutrient absorption. Moreover, achlorhydria after atrophic gastritis may increase the frequency of gastroenteritis, which may be associated with a lower BMI [29].

Table 4 The relationship between body mass index (BMI) and the risk of gastric cancer and dysplasia in males and females

Males							
BMI (kg/m ²)	Controls (n = 628)	Gastric cancer (%) (n = 663)			Gastric dysplasia (%) (n = 214)		
		Cases	Adjusted OR ^a (95 % CI)	P value	Cases	Adjusted OR ^a (95 % CI)	P value
<23	262 (41.7 %)	286 (43.1 %)	1 (ref)		91 (42.5 %)	1 (ref)	
≥ 23 and <25	172 (27.4 %)	193 (29.1 %)	1.254 (0.870–1.809)	0.225	62 (29.0 %)	1.282 (0.758–2.171)	0.354
≥ 25 and <30	180 (28.7 %)	175 (26.4 %)	1.330 (0.920–1.921)	0.129	59 (27.6 %)	1.498 (0.863–2.601)	0.151
≥ 30	14 (2.2 %)	9 (1.4 %)	1.274 (0.421–3.860)	0.668	2 (0.9 %)	1.859 (0.337–10.268)	0.477
			<i>P</i> _{trend}	0.431		<i>P</i> _{trend}	0.485
Females							
BMI (kg/m ²)	Controls (n = 660)	Gastric cancer (%) (n = 335)			Gastric dysplasia (%) (n = 99)		
		Cases	Adjusted OR ^a (95 % CI)	P value	Cases	Adjusted OR ^a (95 % CI)	P value
<23	372 (56.4 %)	182 (54.3 %)	1 (ref)		36 (36.4 %)	1 (ref)	
≥ 23 and <25	161 (24.4 %)	73 (21.8 %)	0.924 (0.598–1.427)	0.720	27 (27.3 %)	1.272 (0.608–2.660)	0.524
≥ 25 and <30	111 (16.8 %)	69 (20.6 %)	1.113 (0.698–1.773)	0.653	28 (28.3 %)	2.086 (1.011–4.302)	0.047
≥ 30	16 (2.4 %)	11 (3.3 %)	0.864 (0.331–2.255)	0.765	8 (8.1 %)	2.713 (0.791–9.306)	0.112
			<i>P</i> _{trend}	0.904		<i>P</i> _{trend}	0.145

Numbers in *italic type* indicate statistical significance

BMI body mass index, OR odds ratio, CI confidence interval, ref reference

^a Logistic model adjusted for age (in years), smoking status, drinking status, family history of gastric cancer, *Helicobacter pylori* infection, atrophic gastritis by histologic evaluation, intestinal metaplasia by histologic evaluation, and serum pepsinogen I/II ratio

H. pylori infection is a well-established risk factor for gastric cancer, and *H. pylori* is classified as a type I carcinogen in humans [30]. *H. pylori* infection is known to increase the risk of gastric noncardia cancer, although no positive relationship between this infection and gastric cardia cancer has been found [31]. It is noteworthy that, according to a recent meta-analysis, *H. pylori* infection may be associated with an increased risk of gastric cardia cancer in high-risk settings such as China, Japan, and Korea, but not in low-risk settings such as Western countries [12]. In addition, two distinct subtypes of cardia cancer have been suggested: reflux-related and *H. pylori*-related [32]. Atrophic gastritis and intestinal metaplasia are known as factors that increase the risk of gastric cancer [33], and many studies have shown that serum pepsinogen I levels and serum pepsinogen I/pepsinogen II ratios are related to gastric atrophy and putatively gastric cancer in clinical settings [20, 34]. A few studies have investigated

the relationships between obesity and *H. pylori* infection [35], gastric atrophy [36], and the serum pepsinogen I/pepsinogen II ratio [37] but produced mixed results. That is, each of these factors has been found to be less or similarly prevalent in obese individuals in comparison with normal ones. To the authors' knowledge, the present study is the first to investigate the relationship between BMI and gastric cancer by adjusting for the *H. pylori* infection status, atrophic gastritis, intestinal metaplasia, and the serum pepsinogen I/pepsinogen II ratio with almost complete coverage of other exposure factors based on a large cohort. A lack of studies considering the *H. pylori* infection status has been one of the major weaknesses in the literature on obesity and gastric cancer. In this study, the status of *H. pylori* infection in all subjects was evaluated by one of four methods, including histologic evaluation, the rapid urease test, *H. pylori* culture, and anti-*H. pylori* immunoglobulin G. The eradication history of *H. pylori* was also

Table 5 The relationship between body mass index (BMI) and the risk of gastric cancer stratified by the gross classification, location, and histologic type of the tumor in males

BMI (kg/m ²)	Controls (n = 628)	Early gastric cancer (%) (n = 393)			Advanced gastric cancer (%) (n = 270)		
		Cases	Adjusted OR ^a (95 % CI)	P value	Cases	Adjusted OR ^a (95 % CI)	P value
<23	262 (41.7 %)	147 (37.4 %)	1 (ref)		139 (51.5 %)	1 (ref)	
≥23 and <25	172 (27.4 %)	124 (31.6 %)	1.514 (0.998–2.296)	0.051	69 (25.6 %)	0.959 (0.604–1.521)	0.858
≥25 and <30	180 (28.7 %)	114 (29.0 %)	1.657 (1.086–2.528)	0.019	61 (22.6 %)	1.045 (0.649–1.682)	0.856
≥30	14 (2.2 %)	8 (2.0 %)	2.372 (0.724–7.768)	0.154	1 (0.4 %)	0.374 (0.042–3.319)	0.377
			<i>P</i> _{trend}	0.057		<i>P</i> _{trend}	0.827
BMI (kg/m ²)	Controls (n = 628)	Gastric noncardia cancer (%) (n = 593)			Gastric cardia cancer (%) (n = 54)		
		Cases	Adjusted OR ^a (95 % CI)	P value	Cases	Adjusted OR ^a (95 % CI)	P value
<23	262 (41.7 %)	249 (42.0 %)	1 (ref)		27 (50.0 %)	1 (ref)	
≥23 and <25	172 (27.4 %)	173 (29.2 %)	1.270 (0.870–1.855)	0.216	15 (27.8 %)	1.363 (0.625–2.973)	0.436
≥25 and <30	180 (28.7 %)	163 (27.5 %)	1.394 (0.954–2.036)	0.086	11 (20.4 %)	1.338 (0.573–3.125)	0.500
≥30	14 (2.2 %)	8 (1.3 %)	1.384 (0.433–4.422)	0.583	1 (1.9 %)	2.169 (0.241–19.493)	0.490
			<i>P</i> _{trend}	0.340		<i>P</i> _{trend}	0.792
BMI (kg/m ²)	Controls (n = 628)	Differentiated histologic type ^b (%) (n = 404)			Undifferentiated histologic type ^c (%) (n = 239)		
		Cases	Adjusted OR ^a (95 % CI)	P value	Cases	Adjusted OR ^a (95 % CI)	P value
<23	262 (41.7 %)	165 (40.8 %)	1 (ref)		112 (46.9 %)	1 (ref)	
≥23 and <25	172 (27.4 %)	125 (30.9 %)	1.396 (0.909–2.144)	0.128	59 (24.7 %)	0.981 (0.610–1.577)	0.937
≥25 and <30	180 (28.7 %)	110 (27.2 %)	1.566 (1.011–2.424)	0.044	63 (26.4 %)	1.110 (0.693–1.777)	0.664
≥30	14 (2.2 %)	4 (1.0 %)	1.254 (0.302–5.210)	0.756	5 (2.1 %)	1.554 (0.416–5.799)	0.512
			<i>P</i> _{trend}	0.202		<i>P</i> _{trend}	0.888

Numbers in *italic type* indicate statistical significance

BMI body mass index, OR odds ratio, CI confidence interval, ref reference

^a Logistic model adjusted for age (in years), smoking status, drinking status, family history of gastric cancer, *Helicobacter pylori* infection, atrophic gastritis by histologic evaluation, intestinal metaplasia by histologic evaluation, and serum pepsinogen I/II ratio

^b Differentiated histologic type refers to well or moderately differentiated carcinoma

^c Undifferentiated histologic type refers to poorly differentiated or signet ring cell carcinomas

Table 6 The relationship between body mass index (*BMI*) and the risk of gastric cancer stratified by the gross classification, location, and histologic type of the tumor in females

BMI (kg/m ²)	Controls (<i>n</i> = 660)		Early gastric cancer (%) (<i>n</i> = 203)		Advanced gastric cancer (%) (<i>n</i> = 132)	
	Cases	Adjusted OR ^a (95 % CI)	<i>P</i> value	Cases	Adjusted OR ^a (95 % CI)	<i>P</i> value
<23	372 (56.4 %)	1 (ref)		86 (65.2 %)	1 (ref)	
≥23 and <25	161 (24.4 %)	1.276 (0.764–2.129)	0.352	24 (18.2 %)	0.600 (0.322–1.121)	0.109
≥25 and <30	111 (16.8 %)	1.538 (0.895–2.643)	0.119	18 (13.6 %)	0.683 (0.346–1.346)	0.271
≥30	16 (2.4 %)	1.188 (0.389–3.629)	0.762	4 (3.0 %)	0.504 (0.124–2.054)	0.339
		<i>P</i> _{trend}	0.456		<i>P</i> _{trend}	0.306
BMI (kg/m ²)	Controls (<i>n</i> = 660)		Gastric noncardia cancer (%) (<i>n</i> = 319)		Gastric cardia cancer (%) (<i>n</i> = 13)	
	Cases	Adjusted OR ^a (95 % CI)	<i>P</i> value	Cases	Adjusted OR ^a (95 % CI)	<i>P</i> value
<23	372 (56.4 %)	1 (ref)		7 (53.8 %)	1 (ref)	
≥23 and <25	161 (24.4 %)	0.980 (0.629–1.528)	0.930	1 (7.7 %)	0.332 (0.039–2.864)	0.316
≥25 and <30	111 (16.8 %)	1.116 (0.692–1.801)	0.653	4 (30.8 %)	1.512 (0.347–6.590)	0.582
≥30	16 (2.4 %)	0.804 (0.295–2.193)	0.670	1 (7.7 %)	3.121 (0.314–31.030)	0.331
		<i>P</i> _{trend}	0.923		<i>P</i> _{trend}	0.447
BMI (kg/m ²)	Controls (<i>n</i> = 660)		Differentiated histologic type ^b (%) (<i>n</i> = 132)		Undifferentiated histologic type ^c (%) (<i>n</i> = 197)	
	Cases	Adjusted OR ^a (95 % CI)	<i>P</i> value	Cases	Adjusted OR ^a (95 % CI)	<i>P</i> value
<23	372 (56.4 %)	1 (ref)		125 (63.5 %)	1 (ref)	
≥23 and <25	161 (24.4 %)	1.784 (0.963–3.306)	0.066	33 (16.8 %)	0.674 (0.392–1.161)	0.155
≥25 and <30	111 (16.8 %)	1.334 (0.671–2.652)	0.411	35 (17.8 %)	1.071 (0.621–1.846)	0.806
≥30	16 (2.4 %)	2.448 (0.776–7.718)	0.127	4 (2.0 %)	0.280 (0.057–1.370)	0.116
		<i>P</i> _{trend}	0.196		<i>P</i> _{trend}	0.197

Numbers in *italic type* indicate statistical significance

BMI body mass index, *OR* odds ratio, *CI* confidence interval, *ref* reference

^a Logistic model adjusted for age (in years), smoking status, drinking status, family history of gastric cancer, *Helicobacter pylori* infection, atrophic gastritis by histologic evaluation, intestinal metaplasia by histologic evaluation, and serum pepsinogen I/II ratio

^b Differentiated histologic type refers to well or moderately differentiated carcinoma

^c Undifferentiated histologic type refers to poorly differentiated or signet ring cell carcinomas

surveyed because past *H. pylori* infection can increase gastric cancer risk even though *H. pylori* is no longer detectable [38]. Through a combination of these comprehensive methods, past as well as current infection was investigated. Therefore, the consideration of data on the *H. pylori* infection status represents an important contribution of this study.

Previous studies of the relationship between obesity and gastric cancer have generally been conducted in Western areas, in which the incidence of gastric cancer is lower and that of gastric cardia cancer is higher than that in Asian countries such as China, Japan, and Korea. Few studies have used Asian data, producing mixed results for the relationship between obesity and gastric cancer, particularly gastric cardia cancer [39–43]. Such mixed results may be explained as follows. First, the incidence of gastric cancer [44] and the prevalence of *H. pylori* infection [45] are higher in Asian countries than in Western ones, whereas the incidence of gastroesophageal reflux disease, Barrett's esophagus [46], or morbid obesity [47] is lower in Asian countries. Second, the incidence of gastric cardia cancer is relatively low in Asia [31]. Third, the rate of overweight or obese patients remains relatively low, and obesity is less severe in Asian countries than in Western ones [47]. These epidemiologic differences between Asian and Western countries may be associated with the development of gastric cancer and may explain the lack of any relationship between obesity and gastric cardia cancer in Asia.

Staging differences related to BMI may be another potential confounding factor explaining the mixed findings of previous studies. In general, patients with gastric cancer tend to be cachexic with low BMIs as gastric cancer progresses to more advanced stages because such patients tend to have gastrointestinal symptoms such as epigastric pain, nausea, and anorexia, particularly in gastric outlet obstruction. Previous studies have shown significant decreased prevalence of T3-4 or N2-3 category cancer in patients with $\text{BMI} \geq 25 \text{ kg/m}^2$, although some studies have provided no relationship between BMI and the stage of gastric cancers [48, 49]. Previous studies suggesting a relationship between obesity and gastric cancers have generally ignored weight change from tumor progression and enrolled patients without considering the stage of their tumor. In the present study, obesity was related to EGC but not to AGC in males.

Previous studies in Western countries have generally classified the BMI for obesity according to the WHO criteria as follows: underweight, below 18.5 kg/m^2 ; normal, 18.5 kg/m^2 to less than 25 kg/m^2 ; overweight, 25 kg/m^2 to less than 30 kg/m^2 ; obese, 30 kg/m^2 to less than 35 kg/m^2 ; morbidly obese, 35 kg/m^2 or greater [50]. In Asia, according to the International Obesity Task Force criteria

for the Asia-Pacific population [21], the BMI criteria for overweight and obesity have been classified as follows: underweight, below 18.5 kg/m^2 ; normal, 18.5 kg/m^2 to less than 23 kg/m^2 ; overweight, 23 kg/m^2 to less than 25 kg/m^2 ; obese, 25 kg/m^2 or greater. For individuals within the same BMI group, Asian populations tend to have a higher percentage of body fat than white or European populations [51]. In the present study, $\text{BMI} \geq 25 \text{ kg/m}^2$, which has been considered an accurate Asian standard, was used as a cutoff point for obesity, and this represents an important contribution of this study.

Only a few studies have addressed the relationship between obesity and gastric dysplasia. A Korean study [52] demonstrated that hyperglycemia and hypercholesterolemia are risk factors in gastric dysplasia, but that BMI is not positively related to gastric dysplasia ($P_{\text{trend}} = 0.845$). Another study suggested a relationship between metabolic syndrome and gastric dysplasia in the general Korean population, but found no significant difference in the mean BMI between gastric dysplasia patients and controls ($P = 0.05$) [17]. However, these studies used fewer enrolled patients with gastric dysplasia than the present study (nearly three times as many cases). In addition, there was a significant relationship between obesity and gastric dysplasia in females even after other risk factors such as the *H. pylori* infection status had been controlled for in the present study.

In most regions, males have a higher age-specific incidence than do females [1]. This difference has been explained by a variation in environmental factors, including *H. pylori* infection, smoking, and different dietary patterns, as well as hormones such as estrogen [25, 53–55]. The finding that there is a significant association between obesity and the risk of EGC and differentiated-type gastric cancer in males but no association in females is intriguing and seems to support a modulatory effect by female sex hormones, although there is no clear evidence for such an effect from experimental studies. Further studies are needed to address this discrepancy in gender.

Our results showed that severe obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) was not significantly associated with the risk of gastric cancer, any subgroup of gastric cancer, and gastric dysplasia. The number of patients with severe obesity might be too small to show the association in the current study.

However, this study has a limitation in that abdominal obesity (waist circumference and the waist-to-hip ratio) and other risk factors in gastric cancer such as physical activity and socioeconomic status were not measured.

In sum, obesity, as measured by the BMI, was related to gastric cancer in the EGC and differentiated-type gastric cancer free from the influence of the *H. pylori* infection status in males. In addition, obesity was related to an increased risk of gastric dysplasia regardless of the *H.*

pylori infection status in females. These results suggest that obesity treatment may help prevent gastric dysplasia and early gastric cancer.

Acknowledgments This work was supported by a National Research Foundation of Korea grant for the Global Core Research Center funded by the Korean government (MSIP) (no. 2011-0030001); however, the authors do not have any conflict of interest. The authors thank the Division of Statistics of the Medical Research Collaborating Center at Seoul National University Bundang Hospital for statistical analyses.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics. *CA Cancer J Clin*. 2013;63:11–30.
2. Steevens J, Botterweck AA, Dirx MJ, van den Brandt PA, Schouten LJ. Trends in incidence of oesophageal and stomach cancer subtypes in Europe. *Eur J Gastroenterol Hepatol*. 2010;22:669–78.
3. Camargo MC, Anderson WF, King JB, Correa P, Thomas CC, Rosenberg PS, et al. Divergent trends for gastric cancer incidence by anatomical subsite in US adults. *Gut*. 2011;60:1644–9.
4. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med*. 2001;345:784–9.
5. Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. *Cancer Causes Control*. 2008;19:689–701.
6. Sung NY, Choi KS, Park EC, Park K, Lee SY, Lee AK, et al. Smoking, alcohol and gastric cancer risk in Korean men: the National Health Insurance Corporation Study. *Br J Cancer*. 2007;97:700–4.
7. Shikata K, Kiyohara Y, Kubo M, Yonemoto K, Ninomiya T, Shirota T, et al. A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. *Int J Cancer*. 2006;119:196–201.
8. McCullough ML, Robertson AS, Jacobs EJ, Chao A, Calle EE, Thun MJ. A prospective study of diet and stomach cancer mortality in United States men and women. *Cancer Epidemiol Biomarkers Prev*. 2001;10:1201–5.
9. Ye W, Chow WH, Lagergren J, Yin L, Nyren O. Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. *Gastroenterology*. 2001;121:1286–93.
10. Botterweck AA, Schouten LJ, Volovics A, Dorant E, van Den Brandt PA. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. *Int J Epidemiol*. 2000;29:645–54.
11. Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. *J Natl Cancer Inst*. 2010;102:1344–53.
12. Cavaleiro-Pinto M, Peleteiro B, Lunet N, Barros H. *Helicobacter pylori* infection and gastric cardia cancer: systematic review and meta-analysis. *Cancer Causes Control*. 2011;22:375–87.
13. Boeing H. Obesity and cancer—the update 2013. *Best Pract Res Clin Endocrinol Metab*. 2013;27:219–27.
14. Chen Y, Liu L, Wang X, Wang J, Yan Z, Cheng J, et al. Body mass index and risk of gastric cancer: a meta-analysis of a population with more than ten million from 24 prospective studies. *Cancer Epidemiol Biomarkers Prev*. 2013;22:1395–408.
15. Turati F, Tramacere I, La Vecchia C, Negri E. A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. *Ann Oncol*. 2013;24:609–17.
16. Lee YJ, Myung SK, Cho B, Park BJ, Park JH, Ju W, et al. Adiposity and the risk of colorectal adenomatous polyps: a meta-analysis. *Cancer Causes Control*. 2011;22:1021–35.
17. Kim HY. Metabolic syndrome is associated with gastric dysplasia. *Eur J Gastroenterol Hepatol*. 2011;23:871–5.
18. Shin CM, Kim N, Lee HS, Lee HE, Lee SH, Park YS, Hwang JH, Kim JW, Jeong SH, Lee DH, Jung HC, Song IS. Validation of diagnostic tests for *Helicobacter pylori* with regard to grade of atrophic gastritis and/or intestinal metaplasia. *Helicobacter*. 2009;14:512–9.
19. Kim SY, Ahn JS, Ha YJ, Doh HJ, Jang MH, Chung SI, et al. Serodiagnosis of *Helicobacter pylori* infection in Korean patients using enzyme-linked immunosorbent assay. *J Immunoassay*. 1998;19:251–70.
20. Kang JM, Kim N, Yoo JY, Park YS, Lee DH, Kim HY, et al. The role of serum pepsinogen and gastrin test for the detection of gastric cancer in Korea. *Helicobacter*. 2008;13:146–56.
21. Low S, Chin MC, Ma S, Heng D, Deurenberg-Yap M. Rationale for redefining obesity in Asians. *Ann Acad Med Singap*. 2009;38:66–9.
22. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer*. 2011;14:113–23.
23. Jung HS, Choi MG, Baeg MK, Lim CH, Kim JS, Cho YK, et al. Obesity is associated with increasing esophageal Acid exposure in Korean patients with gastroesophageal reflux disease symptoms. *J Neurogastroenterol Motil*. 2013;19:338–43.
24. Wu AH, Tseng CC, Bernstein L. Hiatal hernia, reflux symptoms, body size, and risk of esophageal and gastric adenocarcinoma. *Cancer*. 2003;98:940–8.
25. Lindblad M, Rodríguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. *Cancer Causes Control*. 2005;16:285–94.
26. McMillan DC, Sattar N, McArdle CS. ABC of obesity. Obesity and cancer. *BMJ*. 2006;333:1109–11.
27. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet*. 2001;357:539–45.
28. Goodman KJ, Correa P, Mera R, Yezpe MC, Cerón C, Campo C, et al. Effect of *Helicobacter pylori* infection on growth velocity of school-age Andean children. *Epidemiology*. 2011;22:118–26.
29. La Vecchia C. Hypothesis: is the fall in *Helicobacter pylori* related to the global rise in body mass index? *Eur J Cancer Prev*. 2011;20:556.
30. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum*. 1994;60:1–560.
31. Kim JY, Lee HS, Kim N, Shin CM, Lee SH, Park YS, et al. Prevalence and clinicopathologic characteristics of gastric cardia cancer in South Korea. *Helicobacter*. 2012;17:358–68.
32. Hansen S, Vollset SE, Derakhshan MH, Fyfe V, Melby KK, Aase S, et al. Two distinct aetiologies of cardia cancer; evidence from premorbid serological markers of gastric atrophy and *Helicobacter pylori* status. *Gut*. 2007;56:918–25.
33. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process—first American Cancer Society Award Lecture on cancer epidemiology and prevention. *Cancer Res*. 1992;52:6735–40.
34. Kodori A, Yoshihara M, Sumii K, Haruma K, Kajiyama G. Serum pepsinogen in screening for gastric cancer. *J Gastroenterol*. 1995;30:452–60.

35. Kamada T, Hata J, Kusunoki H, Ito M, Tanaka S, Kawamura Y, et al. Eradication of *Helicobacter pylori* increases the incidence of hyperlipidaemia and obesity in peptic ulcer patients. *Dig Liver Dis.* 2005;37:39–43.
36. Torisu T, Matsumoto T, Takata Y, Ansai T, Soh I, Awano S, et al. Atrophic gastritis, but not antibody to *Helicobacter pylori*, is associated with body mass index in a Japanese population. *J Gastroenterol.* 2008;43:762–6.
37. Kutsuma A, Oshida H, Suwa K, Nakajima K. A possible association of low pepsinogen I and pepsinogen I/II with low and high body weight in Japanese men. *Clin Biochem.* 2014;47:126–8.
38. Suzuki H, Iwasaki E, Hibi T. *Helicobacter pylori* and gastric cancer. *Gastric Cancer.* 2009;12:79–87.
39. Jee SH, Yun JE, Park EJ, Cho ER, Park IS, Sull JW, et al. Body mass index and cancer risk in Korean men and women. *Int J Cancer.* 2008;123:1892–6.
40. Inoue M, Noda M, Kurahashi N, Iwasaki M, Sasazuki S, Iso H, et al. Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan. *Eur J Cancer Prev.* 2009;18:240–7.
41. Cho Y, Lee DH, Oh HS, Seo JY, Lee DH, Kim N, et al. Higher prevalence of obesity in gastric cardia adenocarcinoma compared to gastric non-cardia adenocarcinoma. *Dig Dis Sci.* 2012;57:2687–92.
42. Tran GD, Sun XD, Abnet CC, Fan JH, Dawsey SM, Dong ZW, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer.* 2005;113:456–63.
43. Kuriyama S, Tsubono Y, Hozawa A, Shimazu T, Suzuki Y, Koizumi Y, et al. Obesity and risk of cancer in Japan. *Int J Cancer.* 2005;113:148–57.
44. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev.* 2010;19:1893–907.
45. Correa P, Piazuelo MB. Natural history of *Helicobacter pylori* infection. *Dig Liver Dis.* 2008;40:490–6.
46. Wong BC, Kinoshita Y. Systematic review on epidemiology of gastroesophageal reflux disease in Asia. *Clin Gastroenterol Hepatol.* 2006;4:398–407.
47. James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. *Obes Res.* 2001;9(Suppl 4):228S–33S.
48. Ojima T, Iwahashi M, Nakamori M, Nakamura M, Naka T, Ishida K, et al. Influence of overweight on patients with gastric cancer after undergoing curative gastrectomy: an analysis of 689 consecutive cases managed by a single center. *Arch Surg.* 2009;144:351–8 (discussion 358).
49. Inagawa S, Adachi S, Oda T, Kawamoto T, Koike N, Fukao K. Effect of fat volume on postoperative complications and survival rate after D2 dissection for gastric cancer. *Gastric Cancer.* 2000;3:141–4.
50. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:1–253.
51. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet.* 2004;363:157–63.
52. Jung MK, Jeon SW, Cho CM, Tak WY, Kweon YO, Kim SK, et al. Hyperglycaemia, hypercholesterolaemia and the risk for developing gastric dysplasia. *Dig Liver Dis.* 2008;40:361–5.
53. Freedman ND, Derakhshan MH, Abnet CC, Schatzkin A, Hollenbeck AR, McColl KE. Male predominance of upper gastrointestinal adenocarcinoma cannot be explained by differences in tobacco smoking in men versus women. *Eur J Cancer.* 2010;46:2473–8.
54. Camargo MC, Goto Y, Zabaleta J, Morgan DR, Correa P, Rabkin CS. Sex hormones, hormonal interventions, and gastric cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2012;21:20–38.
55. Chandanos E, Lagergren J. Oestrogen and the enigmatic male predominance of gastric cancer. *Eur J Cancer.* 2008;44:2397–403.