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Effect of body-mass index on the risk of gastric cancer: A population-based cohort study in A Japanese population

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ABSTRACT

Background: Body fatness and weight gain are considered probable causes of gastric cancer, specifically in the cardia region. However, limited evidence is available in Asia, where the burden of gastric cancer is high. The objective of this study was to determine an association between body-mass index (BMI) and gastric cancer risk using a large population prospective cohort.

Methods: 92,056 subjects enrolled in the Japan Public Health Center-based prospective Study who reported their height and weight were followed up until the end of 2013. A Cox proportional hazards model was used to estimate the risk for gastric cancer and its subsite based on baseline BMI. A subgroup analysis was conducted taking account of *Helicobacter pylori* (*H. pylori*) infection and atrophic gastritis status.

Results: 2,860 gastric cancer cases (2,047 men, 813 women), 307 proximal gastric cancer cases (244 men, 63 women), and 1967 distal gastric cancer cases (1,405 men, 562 women) were found during the follow-up period. Among men, baseline BMI ≥ 27 kg/m^2 increased the risk of overall gastric cancer (hazards ratio (HR) 1.23, 95% confidence interval (CI) 1.00–1.53). For both sexes, U-shaped increase in the risk was observed for proximal gastric cancer. Subgroup analysis showed a statistically significant association between the risk of proximal gastric cancer and BMI ≥ 27 kg/m^2 among those who were atrophic gastritis positive, *H. pylori* antibody positive, and those who tested positive to either or both atrophic gastritis and *H. pylori* antibody.

Conclusion: Our result suggests that gastric cancer risk increases for men with BMI ≥ 27 kg/m^2.

1. Introduction

Gastric cancer is considered one of the most common cancers, despite a global decreasing trend in incidence [1]. With approximately one million newly diagnosed cases every year, it was ranked as the third most common cause of cancer death in 2018, attributing to 8.2% of cancer-related deaths [1].

General risk factors for gastric cancer are age, male sex, tobacco smoking, radiation, and family history of gastric cancer [2]. Histologically, gastric cancer could be differentiated into two main subtypes – intestinal and diffuse type [3]. Intestinal type gastric cancer is associated with *H. pylori* infection, following the Correa model of gastric carcinogenesis [4], and often found in areas with a high incidence of gastric cancer [5,6]. On the other hand, diffuse type gastric cancer originates from normal gastric mucosa [6], and has been found to be associated with risk factors such as high socioeconomic status (SES) [7], obesity [8,9], and type A blood [10]. Further, gastric cancer could be classified as non–cardia gastric cancer or cardia gastric cancer based on the anatomical location of the lesion [11]. While non-cardia gastric cancer incidence rates are decreasing in Western countries, the incidence rate of cardia gastric cancer has remained constant, suggesting the possibility of different aetiologies [12,13].

Abbreviations: AICR, American Institute for Cancer Research; BMI, body-mass index; CI, confidence interval; CUP, Continuous Update Project; *H. pylori*, *Helicobacter pylori*; HR, hazards ratio; ICD, International Classification of Diseases; IgG, immunoglobulin G; JPHC, Study Japan Public Health Center-based prospective Study; RR, relative risk; WCRF, World Cancer Research Fund; WHO, World Health Organization

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Overweight and obesity, assessed by measures such as body-mass index (BMI) and waist circumference, are more prevalent than ever. It was estimated in 2016 that 1.97 billion adults and over 338 million children and adolescents were categorised as overweight or obese [14]. Obesity increases the risk of chronic diseases as well as mortality [15]. A joint review of the Continuous Update Project (CUP) published by the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) in 2018 suggested that there is strong, convincing evidence that links adult body fatness to esophagus adenocarcinoma, pancreatic, liver, colorectal, postmenopausal breast, endometrium, and kidney cancer [14]. CUP also suggested that obesity may be a probable cause for mouth, pharynx and larynx, gallbladder, ovary, prostate, and cardia gastric cancer [14]. The same report reported a relative risk (RR) of 1.23 (95% confidence interval (CI) 1.07–1.40) of cardia gastric cancer among obese subjects [14]. However, previous studies that assessed the effect of BMI on the long-term outcomes of gastric cancer have conflicting results. While some studies showed an increased risk among obese and overweight subjects [8,9], others found no association [17–19]. Furthermore, many studies were conducted in Western nations, where the burden of gastric cancer is generally low. Determining whether BMI is associated with gastric cancer risk is of a particular interest for East Asian countries including Japan, where the world's third highest gastric cancer incidence is observed [20].

Therefore, we aimed to examine the association between BMI and the risk of gastric cancer in a large population-based prospective cohort study in Japan.

2. Materials and methods

2.1. Study population

The Japan Public Health Center-based Prospective Study (the JPHC Study) [21] is an ongoing prospective cohort. Established in 1990, its objective is to look at what types of lifestyle habits are associated with the onset of diseases. This study used JPHC Study Cohort I and II launched in 1990 and 1993 respectively, including 140,420 registered Japanese men and women aged 40–69 years at the beginning of the baseline survey from 11 public health center areas all over Japan [21]. The details of the study design have been described elsewhere [21]. The participants were informed of the objectives of the study, and those who completed the survey questionnaire were regarded as consenting to participate in the study. The study protocol was approved by the institutional review board of the National Cancer Center, Japan (approval numbers: 2001–021, 2004–059) and The University of Tokyo (approval number: 10508).

2.2. Baseline survey

A questionnaire regarding lifestyle factors was self–administered to 140,420 subjects (68,722 men and 71,698 women) from 11 public health center areas at the baseline of the two cohorts. Participants from two public health center areas (Katsushika (n = 7,097) and Suita (n = 16,427)) were excluded because of the unavailability of complete cancer incidence data. We excluded foreign nationals (n = 51), move out of the study area prior to the study starting point (n = 246), missing age (n = 4), duplicates (n = 10), or those with inadequate follow-up data (n = 81).

We further excluded individuals who did not respond to the baseline questionnaire (n = 21,289), had any previous history of cancer (n = 2,017), failed to provide data on height or body weight (n = 1,065), or implausible response for BMI ($< 14\ kg/m^2$, or $> 40\ kg/m^2$, n = 77), leaving 92,056 individuals (44,122 men and 47,934 women) for the final analysis.

2.3. BMI assessment

Body weight and height of the study participants were self-reported at the beginning of the study. BMI was calculated by dividing the weight by the square of the height (kg/m^2). For the subgroup analysis, BMI was calculated using measured height and weight, measured during the health check-up at the baseline of the study. Previous JPHC Studies have compared the self-reported height and weight with available data from health check-ups [22,23]. Both of these studies reported self-reported BMIs were slightly lower compared with measured BMI, with Spearman correlation coefficients of 0.89 in men and 0.90 in women, suggesting the appropriateness of the self-reported data in the present study. The participants were divided into five BMI categories according to recommended BMI cut-off points for Asian populations; < 19, ≥ 19 to < 23, ≥ 23 to < 25, ≥ 25 to < 27, and $\geq 27\ kg/m^2$ [22].

2.4. Laboratory analysis

H. pylori infection and atrophic gastritis were defined using two biomarkers, *H. pylori* antibody and pepsinogen I and II, respectively. Plasma levels of immunoglobulin G (IgG) were measured using enzyme immunoassay (E Plate "Eiken" *H. pylori* Antibody II; Eiken Kagaku, Tokyo, Japan) [24]. If the IgG titer of *H. pylori* antibody was greater than or equal to 10U/mL, the subject was considered *H. pylori* antibody positive [24]. To determine the plasma levels of pepsinogen I and II, latex agglutination technique was used (LZ test "Eiken" Pepsinogen I, II; Eiken Kagaku, Tokyo, Japan) [24]. A subject was defined as atrophic gastritis positive if pepsinogen I was less or equal to 70 ng/mL, and a ratio of pepsinogen I/II was less or equal to 3.0 [24]. Based on the biomarker results, we separated the study participants into two categories– those who tested negative to both atrophic gastritis and *H. pylori* antibody (atrophic gastritis negative and *H. pylori* antibody negative) and those who tested positive to either or both atrophic gastritis and *H. pylori* antibody (atrophic gastritis and/or *H. pylori* antibody positive).

2.5. Follow–up and identification of gastric cancer cases

Person-years of follow-up were calculated from the date of the baseline survey to the date of gastric cancer diagnosis, move–out from the study area, death, or until December 31st, 2013, whichever came first. The residential registry was used to confirm the residence and survival status of the subjects. The incidence of gastric cancer was identified by active patient notification from major local hospitals in each of the public health center areas, and through linking the record with population-based cancer registries, cancer registries aimed to identify all cases of cancer that occur in a population. Death certificates were used to supplement the information on cancer incidence. Cases of gastric cancer were classified using the International Classification of Diseases (ICD) for Oncology, 3rd edition, codes C16.0–16.9 [25]. A tumour located in the upper position of the stomach was classified as proximal gastric cancer (ICD codes C16.0 – C16.1), while a tumour in the lower position was classified as distal gastric cancer (ICD codes C16.2–16.6). The residual cases were tumours that could not be classified because of overlapping lesions (ICD-O code C16.8) or no information (ICD-O C16.9).

2.6. Statistical analyses

Baseline characteristics were compared based on participants' baseline BMI. Differences in characteristics between categories of BMI were analysed using analysis of variance or χ^2-test. Cox proportional hazards regression models were used to estimate the hazard ratios (HR) and their 95%CI, using attained age as the time scale. ≥ 23 to $< 25\ kg/m^2$ was used as the reference group. The reference category was based on the BMI range which was previously reported to be associated with

the lowest mortality [26]. Covariates were included based on associations found in the previous studies [14,27–31]. Multivariate model adjusted for public health centre areas (nine areas treated as strata), alcohol consumption (continuous), and smoking (never, less than 20 pack-years, greater than or equal to 20 pack-years, missing), family history of gastric cancer (yes or no for parents and siblings), and salt intake (continuous). The associations between BMI and gastric cancer subsites (proximal and distal gastric cancer) were also analysed. The same analyses were conducted after excluding gastric cancer cases occurred within five years from the baseline.

Subgroup analysis was conducted for 19,008 individuals with available data on *H. pylori* infection status and measured BMI. The association between BMI and gastric cancer risk was evaluated among four subgroups: (1) atrophic gastritis positive subjects (2) *H. pylori* antibody positive subjects (3) atrophic gastritis negative and *H. pylori* antibody negative subjects, and (4) atrophic gastritis and/or *H. pylori* antibody positive subjects.

We calculated the p-value for trend by running a regression model including BMI as a continuous variable. All analyses were conducted using Stata version 14.0 (StataCorp LP).

3. Results

During 1,737,355 person-years of follow-up (average 18 years), 2,860 cases of gastric cancer (2,047 men, 813 women), 307 cases of proximal gastric cancer (244 men, 63 women) and 1967 cases of distal gastric cancer (1,405 men, 562 women) were found among 92,056 study participants. Table 1 shows the baseline characteristics of study participants by BMI category for men and women. The mean age was 53.2 ± 7.9 years and 53.6 ± 8.0 for men and women, respectively. A wide discrepancy was observed between genders for drinking and smoking habits. While over half of the study participants who are men were current smokers and drank habitually, the majority of women participants were never smokers (92.3%), and never or past drinkers (88.3%). For both genders, the percentage of current smokers was highest in $< 19\,kg/m^2$ (64.5% for men, 10.1% for women), while the percentage of those who drank over 150 g of ethanol were highest in ≥ 23 to $< 25\,kg/m^2$ (41.6%) and $< 19\,kg/m^2$ (2.5%) for men and women, respectively.

Tables 2 and 3 shows the association between BMI and gastric cancer risk for men and women, respectively. Among men, a borderline significant association was observed for overall gastric cancer among BMI $\geq 27\,kg/m^2$ (HR 1.23, 95%CI 1.00–1.51). When cancer cases within five years of baseline were excluded, the association became statistically significant (HR 1.24, 95%CI 1.01–1.52). For proximal gastric cancer, non-statistical, yet an increase in the risk was observed for both ends of the BMI ($< 19\,kg/m^2$: HR 1.85, 95%CI 0.85–4.02; $\geq 27\,kg/m^2$: HR 1.53, 95%CI 0.84–2.80). No statistical association was observed for overall, proximal, or distal gastric cancer at any of the BMI category for women; however, similar to men, a non-statistical U-shaped increase in the risk was also observed for proximal gastric cancer ($< 19\,kg/m^2$: HR 1.56, 95%CI 0.42–5.69; $\geq 27\,kg/m^2$: HR 1.73, 95%CI 0.70–4.27). The associations did not change even when cancer cases within five years of baseline were excluded.

We conducted a subgroup analysis for 19,008 study participants who had available data on *H. pylori* infection status. Table 4 shows the association between BMI and gastric cancer risk, considering *H. pylori* infection and atrophic gastritis status. Because atrophic gastritis is often considered a sequel of chronic gastritis caused by *H. pylori* infection [32], and due to the small number of tumour cases at some sites, we divided the subjects into four categories based on the results of their blood test.

Among 19,008 participants, 13,592 subjects (71%) tested positive to either or both atrophic gastritis and *H. pylori* antibody. No proximal gastric cancer cases were observed among atrophic gastritis negative and *H. pylori* antibody negative subjects. A statistically significant association between the risk of proximal gastric cancer and BMI $\geq 27\,kg/m^2$ were observed among those who were atrophic gastritis positive (HR 4.84, 95%CI 1.13–20.77), *H. pylori* antibody positive (HR 6.38, 95%CI 1.22–33.32), and atrophic gastritis and/or *H. pylori* antibody positive (HR 4.57, 95%CI 1.07–19.49).

4. Discussion

We believe that this is the first study to investigate the association between BMI and gastric cancer risk by subsite in a large Japanese population cohort, using a suggested BMI cut-off for the Asian population. Furthermore, we looked at the association between gastric cancer and BMI using measured height and weight, taking the status of *H. pylori* infection and atrophic gastritis into consideration.

To our knowledge, there are only two previous cohort studies on the association between gastric cancer and obesity in Japan [33,34]. Kuriyama et al. [33] found no association between overall gastric cancer and obesity for both men and women. While Tanaka et al. [34] found no association between baseline BMI and gastric cancer risk, they found elevated risk of death among subjects who were in the middle and highest tercile BMI at age of 20. Unlike the previous studies, we found a statistically significant increase in the overall gastric cancer risk among men who were BMI $\geq 27\,kg/m^2$, but not for women. Several previous studies have indicated an association between gastric cancer risk and female reproductive hormones [35–37], as well as with pregnancy and delivery history [38]. The rate of gastric cancer increase slowly in women compared with men until the age of 60 or older when women experience menopause [39]. A previous large prospective cohort study conducted in Shanghai suggested a long duration of fertile years and high levels of hormones later in life are inversely associated with gastric cancer risk [40]. The same study showed an increase in gastric cancer risk among postmenopausal women [40]. One possible explanation for this observation is that oestrogen may be interfering with gastric cancer development and progressions [40]. Oestrogen regulates physiological processes through binding to receptors, which are also potent transcriptional regulators [41]. Oestrogen receptors are known to be present in gastric epithelial tissue [42,43] and have been shown to inhibit inflammation [44–46]. Because inflammation plays a key role in gastric cancer development [47–49], it is possible to speculate that oestrogen could be protecting against gastric cancer, which may explain why we did not observe any statistically significant association among women.

When we looked at the association between BMI and gastric cancer subsite, we observed a non-statistical, U-shape increase in proximal gastric cancer risk among BMI $< 19\,kg/m^2$ and $\geq 27\,kg/m^2$ for both men and women. Although there have been some reports on the association between cardia gastric cancer and overweight, the mechanism of how being overweight elevates the risk of gastric cancer remains unclear [50]. The increased risk of gastric cancer among overweight subjects could be explained by the involvement of hormones, such as insulin, insulin-like growth factor axis, adipokines, and sex steroids [51,52]. These biomarkers may be aiding the modulation of cellular proliferation and apoptosis [50]. Another hypothesis is obesity increases intra-abdominal pressure [53], promoting gastroesophageal reflux [54]. This predisposes to Barrett's oesophagus, and ultimately to adenocarcinoma of the gastroesophageal junction [55].

Conversely, there are no studies on the association between low BMI and risk of cardia gastric cancer. Given that smoking is an established risk factor for non-cardia gastric cancer [2], it is possible that our finding is confounded by smoking. When nicotine enters the body, it increases the energy expenditure rapidly, while reducing appetite [56]. This may explain the higher percentage of current smokers in low BMI category. Although we adjusted for smoking status by pack-years, it is possible that we were not able to fully adjust for the effect of smoking on the risk of gastric cancer. *H. pylori* and atrophic gastritis may also be confounding factors for the association between BMI and the risk of proximal gastric cancer among a Japanese population. A French study

Table 1
Characteristics of the study population at baseline by body-mass index (BMI) category, JPHC Study (1990–2013).

	Men (n = 44,122)							Women (n = 47,934)						
		Body-mass index (BMI) (kg/m^2)							Body-mass index (BMI) (kg/m^2)					
	Total	< 19	≥19 - < 23	≥23 - < 25	≥25 - < 27	≥27	*P-trend**	Total	< 19	≥19 - < 23	≥23 - < 25	≥25 - < 27	≥27	*P-trend**
Number of subjects	44,122	1,772	17,761	12,190	7,459	4,940		47,934	2,534	19,720	11,753	7,485	6,442	
Total person-time (person years)	7,98,957.15	28,877.41	3,17,515.96	2,24,461.33	1,38,411.87	89,690.58		9,38,397.91	46,467.47	7,02,435.70	2,32,952.89	1,47,838.96	1,26,218.85	
Age (y, mean ± SD)	53.2 ± 7.9	55.1 ± 8.8	53.6 ± 8.1	53.0 ± 7.8	52.6 ± 7.5	52.1 ± 7.3	< .0001	53.6 ± 8.0	53.6 ± 8.7	53.0 ± 8.0	53.6 ± 7.8	54.4 ± 7.7	54.6 ± 8.0	< .0001
Smoking status (%)														
Never	10,686 (24.2)	300 (16.9)	3,627 (20.4)	3,128 (25.7)	2,128 (28.5)	1,503 (30.4)	< .0001	44,252 (92.3)	2,229 (88.0)	18,184 (92.2)	11,009 (93.7)	6,930 (92.6)	5,900 (91.6)	< .0001
Past	10,295 (23.3)	320 (18.1)	3,687 (20.8)	3,064 (25.1)	1,939 (26.0)	1,285 (26.0)		653 (1.4)	35 (1.4)	239 (1.2)	155 (1.3)	116 (1.5)	108 (1.7)	
Current	22,957 (52.0)	1,144 (64.5)	10,366 (58.4)	5,947 (48.8)	3,365 (45.1)	2,135 (43.2)		2,807 (5.9)	257 (10.1)	1,217 (6.2)	535 (4.5)	396 (5.3)	402 (6.2)	
Missing information	184 (0.4)	8 (0.4)	81 (0.5)	27 (0.4)	27 (0.4)	17 (0.3)		222 (0.5)	13 (0.5)	80 (0.4)	54 (0.5)	43 (0.6)	32 (0.5)	
Ethanol consumption (%)														
Never or past	13,962 (31.6)	681(38.4)	5,464 (30.8)	3,712 (30.5)	2,380 (31.9)	1,724 (34.8)	< .0001	42,348 (88.3)	2,210 (87.2)	15,363 (87.0)	10,430 (88.7)	6,699 (89.4)	5,849 (90.8)	< .0001
Occasional	3,993 (9.0)	105 (5.9)	1,362 (7.7)	1,134 (9.3)	807 (10.8)	585 (11.8)		2,060 (4.3)	94 (3.7)	927 (4.7)	530 (4.5)	292 (3.9)	217 (3.4)	
< 150 g/week	7,259 (16.4)	326 (18.4)	3,179 (17.9)	2,024 (16.6)	1,114 (14.9)	616 (7.0)		2,127 (4.4)	135 (5.3)	1,012 (5.1)	497 (4.2)	299 (4.0)	184 (2.9)	
≥150 g/week	17,908 (40.6)	623 (35.2)	7,343 (41.3)	5,070 (41.6)	2,980 (39.9)	1,892 (38.3)		942 (2.0)	64 (2.5)	428 (2.2)	189 (1.6)	127 (1.7)	134 (2.1)	
Missing information	1,000 (2.3)	36 (2.0)	413 (2.3)	250 (2.0)	178 (2.4)	123 (2.5)		457 (0.9)	31 (1.2)	193 (1.0)	107 (0.9)	68 (0.9)	58 (0.9)	
Gastric cancer cases														
Overall gastric cancer	2,047	96	907	540	303	201		813	49	344	197	123	100	
Proximal gastric cancer	244	12	113	51	43	25		63	6	24	18	5	10	
Distal gastric cancer	1,405	58	607	390	209	141		562	33	248	124	90	67	

SD: standard deviation

* P-for trend: calculated by analysis of variance or χ2-test.

Table 2
Hazard Ratio (HR) and 95% confidence interval (CI) of gastric cancer and subsite according to body-mass index (BMI) for men (n = 44,122), JPHC Study (1990–2013).

			From the baseline				Excluding cancer development within 5 years of the baseline			
	Subjects	Person-time (person years)	Cases	HR	95%CI	*p-trend**	Cases	HR	95%CI	*p-trend**
Gastric cancer										
BMI category (kg/m^2)										
< 19	1,772	28,877.41	96	1.13	(0.84 - 1.51)	< 0.001	69	1.11	(0.82 - 1.49)	< 0.001
≥19 - < 23	17,761	317,515,96	907	1.03	(0.90 - 1.19)		720	1.03	(0.90 - 1.18)	
≥23 - < 25	12,190	224,461.33	540	1 (Ref)			425	1 (Ref)		
≥25 - < 27	7,459	138,411.87	303	0.89	(0.74 - 1.08)		251	0.89	(0.74 - 1.08)	
≥27	4,940	89,690.58	201	1.23	(1.00 - 1.51)		170	1.24	(1.01 - 1.52)	
Total	44,122	798,957.15	2,047				1,635			
Proximal gastric cancer										
BMI category (kg/m^2)										
< 19	1,772	28,877.41	12	1.85	(0.85 - 4.02)	0.16	10	1.84	(0.85 - 4.00)	0.22
≥19 - < 23	17,761	317,515,96	113	1.20	(0.78 - 1.84)		77	1.18	(0.77 - 1.81)	
≥23 - < 25	12,190	224,461.33	51	1 (Ref)			40	1 (Ref)		
≥25 - < 27	7,459	138,411.87	43	1.35	(0.80 - 2.28)		35	1.35	(0.80 - 2.28)	
≥27	4,940	89,690.58	25	1.53	(0.84 - 2.80)		21	1.44	(0.78 - 2.67)	
Total	44,122	798,957.15	244				183			
Distal gastric cancer										
BMI category (kg/m^2)										
< 19	1,772	28,877.41	58	0.94	(0.67 - 1.38)	< 0.001	40	0.93	(0.63 - 1.36)	< 0.001
≥19 - < 23	17,761	317,515,96	607	1.00	(0.85 - 1.18)		475	0.98	(0.83 - 1.16)	
≥23 - < 25	12,190	224,461.33	390	1 (Ref)			299	1 (Ref)		
≥25 - < 27	7,459	138,411.87	209	0.85	(0.66 - 1.07)		167	0.84	(0.67 - 1.06)	
≥27	4,940	89,690.58	141	1.22	(0.96 - 1.57)		114	1.22	(0.95 - 1.57)	
Total	44,122	798,957.15	1,405				1,095			

Cox proportional hazards model was used.
The model included public health center area; alcohol consumption; cigarette pack-years; salt intake; body-mass index (BMI) category; and family history.
* p-for trend was calculated by running a regression model including BMI as a continuous variable.

from 2006 showed *H. pylori* infection was associated with decreased expression of leptin and ghrelin in the stomach and was inversely correlated with elderly participant energy intake and BMI [57]. Given the high prevalence of *H. pylori* among elderly Japanese population [58], we cannot eliminate the possibility of *H. pylori* masking the true association between BMI and proximal gastric cancer risk. While it could be speculated that in Japan, cardia gastric cancer risk may be increased among the low BMI group as well, further studies are

Table 3
Hazard Ratio (HR) and 95% confidence interval (CI) of gastric cancer and subsite according to body-mass index (BMI) for women (n = 47,934), JPHC Study (1990–2013).

			From the baseline				Excluding cancer development within 5 years of baseline			
	Subjects	Person-time (person years)	Cases	HR	95%CI	*p-trend**	Cases	HR	95%CI	*p-trend**
Gastric cancer										
BMI category (kg/m^2)										
< 19	2,534	46,467.47	49	1.21	(0.80 - 1.84)	0.005	35	1.22	(0.81 - 1.86)	0.004
≥19 - < 23	19,720	7,02,425.70	344	1.10	(0.88 - 1.38)		268	1.11	(0.88 - 1.39	
≥23 - < 25	11,753	2,32,952.89	197	1 (Ref)			166	1 (Ref)		
≥25 - < 27	7,485	1,47,838.96	123	1.12	(0.84 - 1.48)		104	1.13	(0.85 - 1.50)	
≥27	6,442	1,26,218.85	100	1.01	(0.74 - 1.38)		78	1.00	(0.74 - 1.37)	
Total	47,934	9,38,397.91	813				651			
Proximal gastric cancer										
BMI category (kg/m^2)										
< 19	2,534	46,467.47	6	1.56	(0.43 - 5.69)	0.71	4	1.55	(0.42 - 5.66)	0.72
≥19 - < 23	19,720	7,02,425.70	24	0.98	(0.44 - 2.17)		19	0.97	(0.44 - 2.15)	
≥23 - < 25	11,753	2,32,952.89	18	1 (Ref)			15	1 (Ref)		
≥25 - < 27	7,485	1,47,838.96	5	0.47	(0.13 - 1.70)		2	0.31	(0.07 - 1.43)	
≥27	6,442	1,26,218.85	10	1.73	(0.70 - 4.27)		9	1.75	(0.71 - 4.33)	
Total	47,934	9,38,397.91	63				49			
Distal gastric cancer										
BMI category (kg/m^2)										
< 19	2,534	46,467.47	33	1.27	(0.76 - 2.14)	0.02	22	1.31	(0.78 - 2.21)	0.01
≥19 - < 23	19,720	7,02,425.70	248	1.25	(0.95 - 1.66)		188	1.27	(0.96 - 1.69)	
≥23 - < 25	11,753	2,32,952.89	124	1 (Ref)			102	1 (Ref)		
≥25 - < 27	7,485	1,47,838.96	90	1.26	(0.89 - 1.78)		73	1.30	(0.92 - 1.84)	
≥27	6,442	1,26,218.85	67	1.07	(0.73 - 1.58)		50	1.05	(0.71 - 1.56)	
Total	47,934	9,38,397.91	562				435			

Cox proportional hazards model was used.
The model included public health center area; alcohol consumption; cigarette pack-years; salt intake; body-mass index (BMI) category; and family history.
* p-for trend was calculated by running a regression model including BMI as a continuous variable.

Table 4
Hazard Ratio (HR) and 95% confidence interval (CI) of gastric cancer and subsite according to body-mass index (BMI) considering *H. pylori* infection and atrophic gastritis status (n = 19,008), JPHC Study (1990–2013).

			Atrophic gastritis positive[a] (n = 8002)				*H. pylori* antibody positive[b] (n = 12,988)				Atrophic gastritis and *H. pylori* infection status combination							
											Atrophic gastritis negative and *H. pylori* antibody negative[c] (n = 5416)				Atrophic gastritis and/or *H. pylori* antibody positive[d] (n = 13,592)			
	Subjects	Person-time (person-years)		HR	95%CI	*p- trend**	Cases	HR	95%CI	*p- trend**	Cases	HR	95%CI	*p- trend**	Cases	HR	95%CI	*p- trend**
Gastric cancer																		
BMI category (kg/m^2)																		
< 19	1,081	18,258.97	29	0.85	(0.45 - 1.60)	0.17	36	1.00	(0.56 - 1.81)	< 0.001	0			0.69	40	1.16	(0.68 - 2.00)	0.17
≥19 - < 23	7,419	1,32,605.09	164	1.13	(0.81 - 1.59)		213	1.39	(1.02 - 1.90)		11	1.65	(0.16 – 16.60)		226	1.35	(1.00 - 1.83)	
≥23 - < 25	4,639	84,114.36	100	1 (Ref)			115	1 (Ref)			3	1 (Ref)			123	1 (Ref)		
≥25 - < 27	3,154	57,778.77	62	1.16	(0.76 - 1.75)		80	1.35	(0.93 - 1.97)		3	3.49	(0.35 – 34.88)		84	1.27	(0.88 - 1.84)	
≥27	2,715	49,772.37	49	1.23	(0.77 - 1.97)		64	1.23	(0.80 - 1.89)		2	1.36	(0.08 – 22.44)		67	1.27	(0.84 - 1.93)	
Total	19,008	3,42,529.55	404				508				19				540			
Proximal gastric cancer																		
BMI category (kg/m^2)																		
< 19	1,081	18,258.97	2	1.26	(0.12 - 12.74)	0.59	2	1.88	(0.16 - 21.33)	0.21	0				2	1.39	(0.14 - 13.66)	0.55
≥19 - < 23	7,419	1,32,605.09	15	1.27	(0.31 - 5.15)		17	2.87	(0.61 – 13.39)		1				19	1.99	(0.53 - 7.39)	
≥23 - < 25	4,639	84,114.36	4	1 (Ref)			4	1 (Ref)			0	1 (Ref)			5	1 (Ref)		
≥25 - < 27	3,154	57,778.77	7	2.14	(0.47 – 9.66)		10	4.24	(0.20 – 22.00)		0				10	2.77	(0.66 -11.68)	
≥27	2,715	49,772.37	5	4.84	(1.13 - 20.77)		5	6.38	(1.22 - 33.32)		0				5	4.57	(1.07 – 19.49)	
Total	19,008	3,42,529.55	33				38								41			
Distal gastric cancer																		
BMI category (kg/m^2)																		
< 19	1,081	18,258.97	19	1.14	(0.56 - 2.55)	0.38	23	1.29	(0.66 - 2.56)	< 0.001	0			0.66	26	1.58	(0.84 - 3.00)	0.2
≥19 - < 23	7,419	1,32,605.09	103	1.29	(0.88 - 2.11)		139	1.50	(1.02 – 2.21)		6	0.9	(0.07 - 11.18)		147	1.54	(1.05 - 2.26)	
≥23 - < 25	4,639	84,114.36	60	1 (Ref)			72	1 (Ref)			3	1 (Ref)			75	1 (Ref)		
≥25 - < 27	3,154	57,778.77	34	0.95	(0.52 - 1.68)		43	1.05	(0.63 - 1.75)		1	1.00	(0.05 – 18.19)		45	1.02	(0.61 - 1.69)	
≥27	2,715	49,772.37	26	0.91	(0.48 - 1.86)		37	0.96	(0.53 – 2.31)		2	1.11	(0.06- 19.74)		39	1.10	(0.63 – 1.94)	
Total	19,008	3,42,529.55	242				314				12				332			

Cox proportional hazards model was used.

The model included public health center area; gender; alcohol consumption; cigarette pack-years; salt intake; body-mass index (BMI) category; family history; *H. pylori* antibody status; and atrophic gastritis status.

[a] Atrophic gastritis positive: Pepsinogen I level ≤70ηg/mL, combined with a ratio of Pepsinogen I and II ≤3.0 L.

[b] *H. pylori* antibody positive: Level serum IgG≥10 U/mL.

[c] Those who tested negative to both atrophic gastritis and *H. pylori* antibody.

[d] Those who tested positive to atrophic gastritis and/or *H. pylori* antibody.

* p-for trend was calculated by running a regression model including BMI as a continuous variable.

necessary to determine the true association.

To evaluate the effect of *H. pylori* infection on the association between BMI and gastric cancer, we conducted a subgroup analysis among 19,008 participants with available *H. pylori* infection data. We saw an increased risk for proximal gastric cancer among atrophic gastritis positive, *H. pylori* antibody seropositive, and atrophic gastritis and/or *H. pylori* antibody positive subjects who were BMI ≥ 27 kg/m^2. For overall gastric cancer and distal gastric cancer, we also observed an increase in the risk among *H. pylori* antibody seropositive and atrophic gastritis and/or *H. pylori* antibody positive subjects who were < 23 kg/m^2. A previous study suggested that a decrease of *H. pylori* infection may result in a higher BMI on the population level, ultimately leading to an increase in the number of cardia gastric cancer cases [59]. Ghrelin, secreted by the stomach, increases when *H. pylori* is eradicated, leading to increased appetite and weight gain [60,61]. Eradication of *H. pylori* has also been proposed to decrease the expression of leptin in the stomach - a study found that a decrease in leptin level in the stomach was also associated with an increase in BMI [62]. Furthermore, atrophic gastritis, caused by *H. pylori* infection, may have a direct effect on the decrease in food intake, as well as on nutrient absorption [54]. Achlorhydria, a condition after atrophic gastritis, may be increasing the gastroenteritis frequency, possibly leading to lower BMI [59]. While our result for proximal gastric cancer did not corroborate with this hypothesis, we also did not have cases among atrophic gastritis negative and *H. pylori* antibody negative subjects. It is therefore difficult to conclude whether the increased risk observed among atrophic gastritis and/or *H. pylori* antibody positive subjects were lower compared to those without the bacteria or gastritis.

To date, only one case-study in Korea [54] looked at the association between BMI and the risk of early gastric cancer and dysplasia, considering *H. pylori* infection status. The study found that obesity (BMI ≥ 25 – < 30 kg/m^2) was associated with increased risk of early gastric cancer (adjusted OR 1.657, 95%CI 1.086–2.528) among men and well- or moderately differentiated adenocarcinoma (adjusted OR 1.566, 95%CI 1.011–2.424). A systematic review conducted in 2011 [63] showed an increase in the risk for cardia gastric cancer (RR 1.98, 95% CI 1.38–2.83) in a stratified analysis for China, Korea, and Japan. Additionally, there are two subtypes of cardia gastric cancer - reflux related and *H. pylori* related [64]. The *H. pylori* related cardia gastric cancer is suggested to develop in a similar pattern to non-cardia gastric cancer [64]. *H. pylori* may be playing a role in cardia gastric cancer development in high-risk settings, but not in low-risk settings.

Overall, the role of *H. pylori* in the development of gastric cancer among obese and overweight patients remains controversial. A long-time follow-up study is required to elucidate the role of obesity in the development of gastric cancer considering *H. pylori* infection status.

The major strength of this study is the utilisation of a prospective cohort. Subjects were recruited from a large sample of the general population, with a high baseline questionnaire response rate (81%) and low loss to follow–up (< 0.1%). With an average of 18 years of follow up, we believe that sufficient cases of gastric cancer were identified for analysis. Using the incidence of gastric cancer as an endpoint rather than death is a strength of this study since it directly measures the risk of gastric cancer. Study participants' atrophic gastritis and *H. pylori* infection status were identified among 21% of the study population using blood tests, increasing the accuracy of *H. pylori* infection diagnosis, enabling subgroup analysis.

There are several limitations. Subjects were recruited mostly in non–metropolitan areas; it may be possible that the results are geographically biased. BMI was calculated using self-reported height and weight. A validation study that looked at the accuracy of self-reported BMI [65] suggested that self-reported weight tends to be underestimated, and this tendency increased as BMI category increased. A Norwegian study that compared self-reported weight and measured weight also showed that women, particularly of those who were obese, tended to under-report their weight [66]. Our findings did not change even when we conducted our subgroup analysis using measured height and weight, suggesting a minimum under- or overestimation of the risk. BMI was measured only at one time point of the study. However, the latent period between being "exposed" to high BMI and the appropriate increase in risk of cancers are unknown. Renehan et al. [67] calculated the geometric mean duration of follow-up in the cohort studies for gastric cancer available for meta-analyses to be 10.8 years, ranging from 7.4 to 16.0 years. Given that our average follow up time is 18 years, it is possible that one point measurement of BMI may have over- or underestimated the risk. We also did not have measurement of central adiposities such as the ratio of the waist-to-hip circumference. Further, given the limited number of cases of proximal gastric cancer and its wide confidence interval, the result of the study may have occurred by chance. We were not able to observe the association between World Health Organization (WHO) defined criteria obesity (BMI > 30 kg/m^2) [68] and gastric cancer risk due to the lack of extremely obese participants in the study. However, given that the prevalence of obesity among Japanese adults is 3.7% in men and 3.5% in women [69], it was not feasible for our analysis to use the cut-off category BMI > 30 kg/m^2. Lastly, there may be additional unmeasured or unknown risk factors such as physical activity [70], blood type [71,72] and occupation [73,74] that may have confounded the association.

In conclusion, our study suggests that overweight may increase the risk of gastric cancer for Japanese men.

Authorship contribution

MI designed the research. MH performed the analysis, prepared the tables, and drafted the paper. MI, ES, and SKA supported the analysis and the finalisation of the paper. NS, ES, SKA, AH, MIw, TY, TS, KS, ST, and MI substantially contributed to the discussion and interpretation of the findings. All authors have read and approved the final manuscript.

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Declaration of Competing Interest

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References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018) 394–424, https://doi.org/10.3322/caac.21492.

[2] P. Karimi, F. Islami, S. Anandasabapathy, N.D. Freedman, F. Kamangar, Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention, Cancer Epidemiol. Biomark. Prev. 23 (5) (2014) 700–713, https://doi.org/10.1158/1055-9965.epi-13-1057.

[3] P. Lauren, The two histological main types of gastric carcinoma: diffuse and so--called intestinal-type carcinoma: an attempt at a histo-clinical classification, Acta Pathol. Microbiol. Scand. 64 (1) (1965) 31–49.

[4] P. Correa, Human gastric carcinogenesis: a multistep and multifactorial process–First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention, Cancer Res. 52 (24) (1992) 6735–6740 Epub 1992/12/15. PubMed PMID: 1458460.

[5] H. Zali, M. Rezaei-Tavirani, M. Azodi, Gastric cancer: prevention, risk factors and treatment, Gastroenterol. Hepatol. Bed Bench. 4 (4) (2011) 175–185 PubMed PMID: 24834180.

[6] R. Sitarz, M. Skierucha, J. Mielko, G.J.A. Offerhaus, R. Maciejewski, W.P. Polkowski, Gastric cancer: epidemiology, prevention, classification, and treatment, Cancer Manag. Res. 10 (2018) 239–248, https://doi.org/10.2147/CMAR.S149619 PubMed PMID: 29445300.

[7] J. Powell, C. McConkey, Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites, Br. J. Cancer 62 (3) (1990) 440.

[8] A.H. Merry, L.J. Schouten, R.A. Goldbohm, P.A. van den Brandt, Body mass index, height and risk of adenocarcinoma of the oesophagus and gastric cardia: a prospective cohort study, Gut 56 (11) (2007) 1503–1511.

[9] M. Lindblad, L.A.G. Rodríguez, J. Lagergren, 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 16 (3) (2005) 285–294.

[10] W. Haenszel, P. Correa, C. Cuello, N. Guzman, L.C. Burbano, H. Lores, et al., Gastric cancer in Colombia. II. Case-control epidemiologic study of precursor lesions, J. Natl. Cancer Inst. 57 (5) (1976) 1021–1026.

[11] A. Colquhoun, M. Arnold, J. Ferlay, K. Goodman, D. Forman, I. Soerjomataram, Global patterns of cardia and non-cardia gastric cancer incidence in 2012, Gut 64 (2015) 1881–1888.

[12] W.F. Anderson, M.C. Camargo, J.F. Fraumeni Jr., P. Correa, P.S. Rosenberg, C.S. Rabkin, Age-specific trends in incidence of noncardia gastric cancer in US adults, JAMA 303 (17) (2010) 1723–1728 Epub 2010/05/06. doi: 10.1001/jama.2010.496. PubMed PMID: 20442388; PubMed Central PMCID: PMCPMC3142962.

[13] S.S. Devesa, J.F. Fraumeni Jr., The rising incidence of gastric cardia cancer, J. Natl. Cancer Inst. 91 (9) (1999) 747–749 Epub 1999/05/18. PubMed PMID: 10328099.

[14] World Cancer Research Fund/American Institute for Cancer Research. Continious Update Project Expert Report 2018, Body fatness and weight gain and the risk of cancer, London, the United Kingdom, 2018.

[15] F. Hu, Obesity epidemiology, Oxford University Press, Oxford; New York, 2008.

[17] M. Rousseau, Parent M-É, J. Siemiatycki, Comparison of self-reported height and weight by cancer type among men from Montreal, Canada, Eur. J. Cancer Prev. 14 (5) (2005) 431–438.

[18] A. Corley, A. Kubo, W. Zhao, Abdominal obesity and the risk of esophageal and gastric cardia carcinomas, Cancer Epidemiol. Biomark. Prev. 17 (2) (2008) 352–358.

[19] K. Sjödahl, C. Jia, L. Vatten, T. Nilsen, K. Hveem, J. Lagergren, Body mass and physical activity and risk of gastric cancer in a population-based cohort study in Norway, Cancer Epidemiol. Biomark. Prev. 17 (1) (2008) 135–140.

[20] J.S.I. Ferlay, M. Ervik, et al., GLOBACAN 2012 v1.0, cancer incidence and mortality worldwide IARC CancerBase No.11, (2017) [cited 2017]..

[21] S. Tsugane, N. Sawada, The JPHC study: design and some findings on the typical Japanese diet, Jpn. J. Clin. Oncol. 44 (9) (2014) 777–782, https://doi.org/10.1093/jjco/hyu096.

[22] M. Inoue, T. Sobue, S. Tsugane, Impact of body mass index on the risk of total cancer incidence and mortality among middle-aged Japanese: data from a large-scale population-based cohort study – the JPHC study, Cancer Causes Control 15 (7) (2004) 671–680, https://doi.org/10.1023/b:Caco.0000036177.77953.47.

[23] S. Tsugane, S. Sasaki, Y. Tsubono, Under- and overweight impact on mortality among middle-aged Japanese men and women: a 10-y follow-up of JPHC study cohort I, Int. J. Obesity Related Metab. Disord. 26 (4) (2002) 529–537 Epub 2002/06/22. PubMed PMID: 12075580.

[24] H. Charvat, S. Sasazuki, M. Inoue, M. Iwasaki, N. Sawada, T. Shimazu, et al., Prediction of the 10-year probability of gastric cancer occurrence in the Japanese population: the JPHC study cohort II, Int. J. Cancer (2015), https://doi.org/10.1002/ijc.29705 PubMed PMID: 26219435.

[25] A. Fritz, International Classification of Diseases for Oncology: ICD-O, 3rd ed., World Health Organization, Geneva, 2000.

[26] D. Aune, A. Sen, M. Prasad, T. Norat, I. Janszky, S. Tonstad, et al., Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents, Lancet (London, England) 388 (10046) (2016) 776–786, https://doi.org/10.1016/s0140-6736(16)30175-1 PubMed PMID: 27423262; PubMed Central PMCID: PMCPMC4995441.

[27] J. Tredaniel, P. Boffetta, E. Buiatti, R. Saracci, A. Hirsch, Tobacco smoking and gastric cancer: review and meta-analysis, Int. J. Cancer 72 (4) (1997) 565–573 Epub 1997/08/07. PubMed PMID: 9259392.

[28] J.L. Huret, M. Ahmad, M. Arsaban, A. Bernheim, J. Cigna, F. Desangles, et al., Atlas of genetics and cytogenetics in oncology and haematology in 2013, Nucleic Acids Res. 41 (2013) (Database issue):D920-4. Epub 2012/11/20. doi: 10.1093/nar/gks1082. PubMed PMID: 23161685; PubMed Central PMCID: PMCPMC3531131.

[29] S. Singh, J.E. Varayil, S. Devanna, M.H. Murad, P.G. Iyer, Physical activity is associated with reduced risk of gastric cancer: a systematic review and meta-analysis, Cancer Prev. Res. 7 (1) (2014) 12–22, https://doi.org/10.1158/1940-6207.Capr-13-0282.

[30] B. Peleteiro, C. Lopes, C. Figueiredo, N. Lunet, Salt intake and gastric cancer risk according to Helicobacter pylori infection, smoking, tumour site and histological type, Br. J. Cancer 104 (1) (2011) 198–207 Epub 2010/11/16. doi: 10.1038/sj.bjc.6605993. PubMed PMID: 21081930.

[31] M. Rota, C. Pelucchi, P. Bertuccio, K. Matsuo, Z.-F. Zhang, H. Ito, et al., Alcohol consumption and gastric cancer risk—a pooled analysis within the StoP project consortium, Int. J. Cancer 141 (10) (2017) 1950–1962, https://doi.org/10.1002/ijc.30891.

[32] P.E. Arkkila, K. Seppala, M.A. Farkkila, L. Veijola, P. Sipponen, Helicobacter pylori eradication in the healing of atrophic gastritis: a one-year prospective study, Scand. J. Gastroenterol. 41 (7) (2006) 782–790 Epub 2006/06/21. doi: 10.1080/00365520500463175. PubMed PMID: 16785190.

[33] S. Kuriyama, Y. Tsubono, T. Shimazu, Y. Suzuki, Y. Koizumi, Y. Suzuki, et al., Obesity and risk of cancer in Japan, Int. J. Cancer 113 (1) (2005) 148–157, https://doi.org/10.1002/ijc.20529.

[34] T. Tanaka, C. Nagata, S. Oba, N. Takatsuka, H. Shimizu, Prospective cohort study of body mass index in adolescence and death from stomach cancer in Japan, Cancer Sci. 98 (11) (2007) 1785–1789, https://doi.org/10.1111/j.1349-7006.2007.00583.x.

[35] H. Furukawa, T. Iwanaga, H. Koyama, H. Taniguchi, Effect of sex hormones on carcinogenesis in the stomachs of rats, Cancer Res. 42 (12) (1982) 5181–5182.

[36] C.W. Wu, C.W. Chi, T.J. Chang, W.Y. Lui, F.K. P'eng, Sex hormone receptors in gastric cancer, Cancer 65 (6) (1990) 1396–1400.

[37] S. Singh, R. Poulsom, N. Wright, M. Sheppard, M. Langman, Differential expression of oestrogen receptor and oestrogen inducible genes in gastric mucosa and cancer, Gut 40 (4) (1997) 516–520.

[38] H. Furukawa, T. Iwanaga, M. Hiratsuka, S. Imaoka, O. Ishikawa, T. Kabuto, et al., Gastric cancer in young adults: growth accelerating effect of pregnancy and delivery, J. Surg. Oncol. 55 (1) (1994) 3–6.

[39] P. Sipponen, P. Correa, Delayed rise in incidence of gastric cancer in females results in unique sex ratio (M/F) pattern: etiologic hypothesis, Gastric Cancer 5 (4) (2002) 213–219 Epub 2002/12/20. doi: 10.1007/s101200200037. PubMed PMID: 12491079.

[40] N.D. Freedman, W.-H. Chow, Y.-T. Gao, X.-O. Shu, B.-T. Ji, G. Yang, et al., Menstrual and reproductive factors and gastric cancer risk in a large prospective study of women, Gut 56 (12) (2007) 1671–1677 Epub 2007/07/12. doi: 10.1136/gut.2007.129411. PubMed PMID: 17627962.

[41] D.J. Mangelsdorf, C. Thummel, M. Beato, P. Herrlich, G. Schutz, K. Umesono, et al., The nuclear receptor superfamily: the second decade, Cell 83 (6) (1995) 835–839 Epub 1995/12/15. doi: 10.1016/0092-8674(95)90199-x. PubMed PMID: 8521507; PubMed Central PMCID: PMCPMC6159888.

[42] D. Karat, I. Brotherick, B.K. Shenton, D. Scott, S.A. Raimes, S.M. Griffin, Expression of oestrogen and progesterone receptors in gastric cancer: a flow cytometric study, Br. J. Cancer 80 (8) (1999) 1271–1274 Epub 1999/06/22. doi: 10.1038/sj.bjc.6990497. PubMed PMID: 10376983; PubMed Central PMCID: PMCPMC2362374.

[43] N. Takano, N. Iizuka, S. Hazama, S. Yoshino, A. Tangoku, M. Oka, Expression of estrogen receptor-alpha and -beta mRNAs in human gastric cancer, Cancer Lett. 176 (2) (2002) 129–135 Epub 2002/01/24. doi: 10.1016/s0304-3835(01)00739-x. PubMed PMID: 11804739.

[44] K. De Bosscher, W. Vanden Berghe, G. Haegeman, Cross-talk between nuclear receptors and nuclear factor kappaB, Oncogene 25 (51) (2006) 6868–6886 Epub 2006/10/31. doi: 10.1038/sj.onc.1209935. PubMed PMID: 17072333.

[45] D. Kalaitzidis, T.D. Gilmore, Transcription factor cross-talk: the estrogen receptor and NF-kappaB, Trends Endocrinol. Metab. 16 (2) (2005) 46–52 Epub 2005/03/01. doi: 10.1016/j.tem.2005.01.004. PubMed PMID: 15734144.

[46] J. Pfeilschifter, R. Koditz, M. Pfohl, H. Schatz, Changes in proinflammatory cytokine activity after menopause, Endocr. Rev. 23 (1) (2002) 90–119 Epub 2002/02/15. doi: 10.1210/edrv.23.1.0456. PubMed PMID: 11844745.

[47] P. Correa, W. Haenszel, C. Cuello, S. Tannenbaum, M. Archer, A model for gastric cancer epidemiology, Lancet (London, England) 2 (7924) (1975) 58–60 Epub 1975/07/12. doi: 10.1016/s0140-6736(75)90498-5. PubMed PMID: 49653.

[48] P. Correa, The biological model of gastric carcinogenesis, IARC Sci. Publ. 157 (2004) 301–310 Epub 2004/04/02. PubMed PMID: 15055303.

[49] J.G. Fox, T.C. Wang, Inflammation, atrophy, and gastric cancer, J. Clin. Invest. 117 (1) (2007) 60–69 Epub 2007/01/04. doi: 10.1172/jci30111. PubMed PMID: 17200707; PubMed Central PMCID: PMCPMC1716216.

[50] J. Fan, Body mass index and risk of gastric cancer: a 30-year follow-up study in the Linxian general population trial cohort, Cancer Sci. 108 (8) (2017) 1667–1672, https://doi.org/10.1111/cas.13292 PubMed PMID: 28594442; PubMed Central PMCID: PMCPMC5543512.

[51] D.C. McMillan, N. Sattar, C.S. McArdle, ABC of obesity. Obesity and cancer, BMJ 333 (7578) (2006) 1109–1111, https://doi.org/10.1136/bmj.39042.565035.BE1 Epub 2006/11/25. PubMed PMID: 17124223; PubMed Central PMCID: PMCPMC1661751.

[52] E.E. Calle, R. Kaaks, Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms, Nat. Rev. Cancer 4 (8) (2004) 579–591, https://doi.org/10.1038/nrc1408 PubMed PMID: 15286738.Epub 2004/08/03.

[53] H.S. Jung, M.G. Choi, M.K. Baeg, C.H. Lim, J.S. Kim, Y.K. Cho, et al., Obesity is associated with increasing esophageal Acid exposure in korean patients with gastroesophageal reflux disease symptoms, J. Neurogastroenterol. Motil. 19 (3) (2013) 338–343, https://doi.org/10.5056/jnm.2013.19.3.338 PubMed PMID: 23875101.

[54] H.J. Kim, N. Kim, H.Y. Kim, H.S. Lee, H. Yoon, C.M. Shin, et al., Relationship between body mass index and the risk of early gastric cancer and dysplasia regardless of Helicobacter pylori infection, Gastric Cancer 18 (4) (2015) 762–773, https://doi.org/10.1007/s10120-014-0429-0.

[55] A.H. Wu, C.C. Tseng, L. Bernstein, Hiatal hernia, reflux symptoms, body size, and risk of esophageal and gastric adenocarcinoma, Cancer 98 (5) (2003) 940–948, https://doi.org/10.1002/cncr.11568 PubMed PMID: 12942560.Epub 2003/08/28.

[56] J. Audrain-McGovern, N.L. Benowitz, Cigarette smoking, nicotine, and body weight, Clin. Pharmacol. Ther. 90 (1) (2011) 164–168, https://doi.org/10.1038/

clpt.2011.105 PubMed PMID: 21633341; PubMed Central PMCID: PMCPMC3195407.Epub 2011/06/03.
[57] N. Salles, A. Menard, A. Georges, M. Salzmann, V. de Ledinghen, A. de Mascarel, et al., Effects of Helicobacter pylori infection on gut appetite peptide (leptin, ghrelin) expression in elderly inpatients, J. Gerontol. Ser. A Biol. Sci. Med. Sci. 61 (11) (2006) 1144–1150 Epub 2006/12/15. PubMed PMID: 17167154.
[58] M. Inoue, Changing epidemiology of Helicobacter pylori in Japan, Gastric Cancer 20 (1) (2017) 3–7, https://doi.org/10.1007/s10120-016-0658-5.
[59] C. La Vecchia, Hypothesis: is the fall in Helicobacter pylori related to the global rise in body mass index? Eur. J. Cancer Prev. 20 (6) (2011) 556, https://doi.org/10.1097/CEJ.0b013e32834a8018 PubMed PMID: 00008469-201111000-00016.
[60] H. Osawa, M. Nakazato, Y. Date, H. Kita, H. Ohnishi, H. Ueno, et al., Impaired production of gastric ghrelin in chronic gastritis associated with Helicobacter pylori, J. Clin. Endocrinol. Metab. 90 (1) (2005) 10–16, https://doi.org/10.1210/jc.2004-1330 PubMed PMID: 15483107.Epub 2004/10/16.
[61] A. Tatsuguchi, K. Miyake, K. Gudis, S. Futagami, T. Tsukui, K. Wada, et al., Effect of Helicobacter pylori infection on ghrelin expression in human gastric mucosa, Am. J. Gastroenterol. 99 (11) (2004) 2121–2127, https://doi.org/10.1111/j.1572-0241.2004.30291.x PubMed PMID: 15554990.Epub 2004/11/24.
[62] T. Azuma, H. Suto, Y. Ito, M. Ohtani, M. Dojo, M. Kuriyama, et al., Gastric leptin and Helicobacter pylori infection, Gut 49 (3) (2001) 324–329 Epub 2001/08/21. PubMed PMID: 11511551; PubMed Central PMCID: PMCPMC1728440.
[63] M. Cavaleiro-Pinto, B. Peleteiro, N. Lunet, H. Barros, Helicobacter pylori infection and gastric cardia cancer: systematic review and meta-analysis, Cancer Causes Control 22 (3) (2011) 375–387, https://doi.org/10.1007/s10552-010-9707-2.
[64] S. Hansen, S.E. Vollset, M.H. Derakhshan, V. Fyfe, K.K. Melby, S. Aase, et al., Two distinct aetiologies of cardia cancer; evidence from premorbid serological markers of gastric atrophy and Helicobacter pylori status, Gut 56 (7) (2007) 918–925, https://doi.org/10.1136/gut.2006.114504.
[65] M.A. Gosse, How accurate is self-reported BMI? Nutr. Bull. 39 (1) (2014) 105–114, https://doi.org/10.1111/nbu.12075.
[66] G. Skeie, N. Mode, M. Henningsen, K.B. Borch, Validity of self-reported body mass index among middle-aged participants in the Norwegian Women and Cancer study, Clin. Epidemiol. 7 (2015) 313–323, https://doi.org/10.2147/CLEP.S83839 PubMed PMID: 26170718.
[67] A.G. Renehan, M. Tyson, M. Egger, R.F. Heller, M. Zwahlen, Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies, Lancet (London, England) 371 (9612) (2008) 569–578, https://doi.org/10.1016/s0140-6736(08)60269-x PubMed PMID: 18280327.Epub 2008/02/19.
[68] World Health Organization, West Pacific Region. The Asia-Pacific Perspective; Redefinding Obesity and Its Treatment, [cited 2018]. Available from: World Health Organization, Geneva, 2000http://www.wpro.who.int/nutrition/documents/Redefining_obesity/en/.
[69] Japan National Health and Nutrition Survey, Japan Ministry of Health, Labour and Welfare (Japan), National Institute of Health and Nutirion (Japan), 2012.
[70] P.T. Campbell, M. Sloan, N. Kreiger, Physical activity and stomach cancer risk: the influence of intensity and timing during the lifetime, Eur. J. Cancer (Oxford, England: 1990) 43 (3) (2007) 593–600, https://doi.org/10.1016/j.ejca.2006.11.011 PubMed PMID: 17222548.Epub 2007/01/16.
[71] L.C. Hoskins, H.A. Loux, A. Britten, N. Zamcheck, Distribution of ABO blood groups in patients with pernicious anemia, gastric carcinoma and gastric carcinoma associated with pernicious anemia, New Engl. J. Med. 273 (12) (1965) 633–637, https://doi.org/10.1056/nejm196509162731204 PubMed PMID: 5826425.Epub 1965/09/16.
[72] G. Edgren, H. Hjalgrim, K. Rostgaard, R. Norda, A. Wikman, M. Melbye, et al., Risk of gastric cancer and peptic ulcers in relation to ABO blood type: a cohort study, Am. J. Epidemiol. 172 (11) (2010) 1280–1285, https://doi.org/10.1093/aje/kwq299 PubMed PMID: 20937632.Epub 2010/10/13..
[73] A. Raj, J.F. Mayberry, T. Podas, Occupation and gastric cancer, Postgrad. Med. J. 79 (931) (2003) 252–258 Epub 2003/06/05. PubMed PMID: 12782770; PubMed Central PMCID: PMCPMC1742699.
[74] K. Straif, L. Chambless, S.K. Weiland, A. Wienke, M. Bungers, D. Taeger, et al., Occupational risk factors for mortality from stomach and lung cancer among rubber workers: an analysis using internal controls and refined exposure assessment, Int. J. Epidemiol. 28 (6) (1999) 1037–1043 Epub 2000/02/08. PubMed PMID: 10661645.