P.O.Box 2345, Beijing 100023,China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

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• GASTRIC CANCER •

Effect of body mass index on adenocarcinoma of gastric cardia

Ji Zhang, Xiang-Qian Su, Xiao-Jiang Wu, Ya-Hang Liu, Hua Wang, Xiang-Nong Zong, Yi Wang, Jia-Fu Ji

Ji Zhang, Xiang-Qian Su, Xiao-Jiang Wu, Xiang-Long Zong, Yi Wang, Jia-Fu Ji, Department of Surgery, Beijing Cancer Hospital, Beijing Institute of Cancer Research, School of Oncology, Peking University, Beijing 100036, China
Ya-Hang Liu, Hua Wang, Department of Surgery, 1st Teaching Hospital, Inner Mongolian Medical School, Hohhot 010005, Inner Mongolia Autonomous Region, China
Supported by the National High Technology Research and Development Program of China (863 Program), No.2001AA227101
Correspondence to: Professor Jia-Fu Ji, Department of Surgery, Beijing Cancer Hospital, Beijing Institute of Cancer Research, School of Oncology, Peking University, Beijing 100036, China. jiafuj@hotmail.com
Telephone: +86-10-88121122-2048 **Fax:** +86-10-88121122-2049
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Abstract

AIM: Obesity has been proved as one of the main risk factors for gastric cardia adenocarcinoma (GCA) in the West. The objective of our research was to evaluate the relationship between obesity and the risk of GCA in people from North China.

METHODS: A total of 300 patients who had been diagnosed as GCA and had accepted surgical operation at Beijing Cancer Hospital from 1995 to 2002 were enrolled. Data were collected from pathology materials and hospital records. Two hundred and fifty-eight healthy people who had accepted health examination at the same hospital during the same period were enrolled as controls. Height, weight and gender of them at the time of examination were also collected. Obesity was estimated by body mass index (BMI), computed as weight in kilograms per square surface area (Kg/m^2). The degree of obesity was determined by using BMI$\leqslant$18.5, 24-27.9 and $\geqslant$28 (Kg/m^2) as the cut-off points for underweight/normal, overweight and obesity, respectively. Associations with obesity were estimated by odds ratios (ORs) and 95 % confidence intervals (CIs). All ORs were adjusted for age and sex.

RESULTS: The mean level of BMI was significantly lower in the patient group than that in the control group. The ORs for obesity in age groups 30-59 and 60-79 were 1.15 (95 % CI=0.37-3.65) and 0.16 (95 % CI=0.05-0.44) for males and 0.78 (95 % CI=0.26-2.36) and 0.28 (95 % CI=0.04-2.05) for females, respectively. The ORs for underweight were 2.42 (95 % CI=0.56-10.53) and 4.68 (95 % CI=1.13-19.40) for males in age subgroups 30-59 and 60-79 and 40.7 (95 % CI=9.32-177.92) for females older than 60 yrs. BMI was significantly associated with GCA ($P<0.01$). Underweight people were at high risk for GCA.

CONCLUSION: BMI is an independent risk factor for GCA. Underweight is positively associated with GCA.

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INTRODUCTION

The incidence of gastric cardia adenocarcinoma (GCA) has been rising steadily over the past two decades in the United States and Western Europe[1-6]. Extensive studies have been conducted, trying to find its etiological reasons. Some studies showed that the risk for GCA was higher in obese people than that in normal counterparts. It has been generally accepted that obesity is one of the main risk factors for GCA[7-9]. Of all the hypotheses explaining the association between obesity and GCA, reflux theory is the widely accepted one[10-17]. Based on this theory, obesity can promote gastroesophageal reflux disease by increasing intra-abdominal pressure. Gastroesophageal reflux predisposes to Barrett' s esophagus which is a metaplastic precursor state for GCA[18-23]. But the reflux theory cannot explain every aspect of the manifestations of GCA. The real mechanism underlying the disease is still unclear.

We are still unaware if the incidence of GCA has the same pattern in China as in Western world. Based on previous studies, we know that GCA is not rare in China[24]. Great differences exist in life styles and diet habits between Chinese and the Westerners. Elucidating the association between obesity and GCA among Chinese people will be very helpful for prevention and early diagnosis of the disease. The objectives of our study were to investigate whether obesity was more prevalent in patients with GCA than in healthy people, whether the risk for GCA was greater in obese people than in non-obese counterparts, and whether obesity was a dependent/independent risk factor for GCA.

We used body mass index (BMI) to evaluate the degree of obesity. In Western world, the cut-off points of BMI for overweight and obesity are 25 kg/m^2 and 30 mg/m^2. The Chinese people are relatively lean. It is not appropriate to use the same criteria. Recently, a population-based investigation was conducted[25,26] by Zhou *et al* in China. Their results suggested that the cut-off points of BMI for underweight, overweight and obesity of the Chinese people were 18.5 kg/m^2, 24 kg/m^2 and 28 kg/m^2. We used the later criteria in our study.

MATERIALS AND METHODS

Materials

Three hundred patients were enrolled to receive radical operation for GCA in the Department of Surgery at Beijing Cancer Hospital from January 1, 1995 to December 31, 2002. All the hospital records and pathologic materials of these patients were reviewed. The inclusion criteria were listed as follows: The patients were 30 years old or older and the diagnosis of GCA was confirmed by pathologic examinations (reviewed by two independent pathologists). Classification was based on Dr. Siewert' s criteria for gastric cardia carcinoma[27].

The exclusion criteria were stipulated as follows: (1) The patients had a history of malignancies other than GCA; (2) The patients had a history of wasting disease before the diagnosis of the studied malignancy; (3) Adenocarcinoma was not diagnosed as the only histological type of the original malignancy; (4) The patients had a history of gastric cancer and received radical partial gastrectomy. The GCA arose from his/her gastric remnant.

Two hundred and fifty-eight residents who received health examination at Beijing Cancer Hospital from January 1, 2000 to December 31, 2002 were enrolled as healthy control subjects. All the healthy subjects were 30 years old or older, and had no history of any wasting disease. Pregnant women were not included in this study.

Methods

Data, including age, gender, height, weight of the patients and control subjects, were collected. For all patients who experienced weight loss during the disease, their usual height and weight before the disease were also collected. Patients whose hospital records could not provide all the information were not included in this study.

Obesity was measured by BMI, and computed as weight in kilograms per square surface area in square meters (kg/m^2). The height and weight before the disease were used to compute the BMI for patients who had experienced weight loss before the diagnosis was confirmed. The patients and control subjects of the same gender were compared with their mean values of BMI. The patients and control subjects were subdivided into five 10-year age subgroups (age 30-39, 40-49, 50-59, *etc.*). All the subjects were also divided into 2 age subgroups, age $\leqslant$60 yrs or age >60 yrs. Mean values of BMI were compared between patients and control subjects in the same age subgroup.

According to their value of BMI, all the subjects were subdivided into four subgroups (underweight, normal, overweight and obesity) using 18.5, 24 and 28 as the cut-off points of BMI for underweight, overweight and obesity. Relative risks of each group were estimated by odds ratios (ORs) and 95 % confidence intervals (CIs).

Statistic analysis of the data was performed using Chi-square test, with a level of significance at $P\leqslant0.05$. Monte Carlo estimate was used to balance the differences in age and sex structure between the two groups. Lastly, we used logistic regression to evaluate whether obesity was an independent risk factor for GCA.

RESULTS

A total of 300 patients, including 51 women and 249 men, aged 34-80 yrs (median 61.9 yrs), and 258 healthy control subjects (144 women and 114 men) aged 31-78 yrs (median 53.57 yrs), were finally enrolled. The age and sex structure of the patient group differed significantly from those of the control group ($P<0.01$).

The mean value of BMI was 22.90 kg/m^2 in the patient group and 24.85 kg/m^2 in the control group. In each coordinated sex or age subgroup, patients tended to have a low level of BMI than healthy control subjects (Table 1 and Table 2). After sex and age structures were balanced, the mean value of BMI was significantly lower in the patients group than that in the healthy control group ($P<0.01$).

Table 1 Mean levels of BMI in each age group of patients and healthy control subjects

Age	Patient group		Control group	
	Number of cases	Median level of BMI	Number of cases	Median level of BMI
30-39	8	21.94	50	24.26
40-49	27	22.37	69	25.54
50-59	84	22.64	55	24.71
60-69	134	23.46	54	24.93
70-79	47	22.25	30	24.38
Total	300	22.90	258	24.85

Table 2 Mean levels of BMI in each sex group of patients and healthy control subjects

Gender	Patient group		Control group	
	Number of cases	Median level of BMI	Number of cases	Median level of BMI
Male	249	22.88	115	24.75
Female	51	23.02	143	24.94
Total	300	22.90	258	24.85

After all the subjects were labeled as underweight, normal, overweight or obesity based on their BMI, the odds ratios and 95 % confidence intervals in each BMI subgroup were calculated. We used Monte Carlo estimate to balance the differences in age and sex between the two groups, 60 yrs as the cut-off point for age subdivision. In each coordinated subgroup, high BMI people did not show any elevated risk for GCA compared with low BMI ones. On the contrary, the relative risk for GCA rose significantly when the BMI of the subject reached the underweight criteria, especially in women older than 60 yrs ($P<0.05$ by Fisher' s exact test). The risk did not show significant differences only in men of 60 yrs old and younger (Table 3 and Table 4).

Table 3 Odds ratios (ORs) and 95 % confidence intervals (CIs) with body mass index (BMI) by age and sex

Age	Sex	BMI group	Studied group		Total	ORs	95 %	CIs
			Control	Patient				
1[a]	Male	UW[c]	2	16	18	2.42	0.56	10.53
		NM[d]	19	84	103	1.55	0.80	3.03
		OW[e]	20	42	62	0.45	0.23	0.89
		OB[f]	4	16	20	1.15	0.37	3.65
		TOTAL	45	158	203			
	Female	UW	0	5	5	-	-	-
		NM	18	12	30	1.01	0.40	2.55
		OW	18	8	26	0.56	0.21	1.49
		OB	11	6	17	0.78	0.26	2.36
		TOTAL	47	31	78			
2[b]	Male	UW	2	11	13	4.68	1.13	19.40
		NM	26	45	71	1.66	0.88	3.13
		OW	26	31	57	0.87	0.46	1.68
		OB	16	4	20	0.16	0.05	0.44
		TOTAL	70	91	161			
	Female	UW	1	6	7	40.7	9.32	177.92
		NM	45	7	52	0.61	0.22	1.66
		OW	35	6	41	0.75	0.26	2.12
		OB	15	1	16	0.28	0.04	2.05
		TOTAL	96	20	116			

a. Age group 1: $\leqslant$60 yrs, b. Age group 2: >60 yrs, c. UW=underweight (BMI<18.5 kg/m^2), d. NM=Normal (18.5$\leqslant$ BMI<24 kg/m^2), e. OW=Overweight (24$\leqslant$BMI<28 kg/m^2), f. OB=Obesity (BMI$\geqslant$28 kg/m^2).

Table 4 Fisher's exact test for evaluation of significance of association between underweight and high relative risk for GCA

Age	Sex	χ^2 value	*P*	Monte carlo sig. (2-sided) 99 % confidence interval	
				Lower bound	Upper bound
1[a]	Male	5.357	0.136	0.127	0.144
	Female	8.161	0.036	0.031	0.041
2[b]	Male	16.438	0.001	0.000	0.002
	Female	17.196	0.001	0.000	0.001

a. Age Group 1: $\leqslant$60 yrs, b. Age Group 2: >60 yrs.

Compared with age, sex, previous gastrointestinal disease history and family history of gastric cancer, MBI showed itself to be an independent risk factor for GCA (Table 5, Table 6) (P<0.01).

Table 5 Logistic regression analysis of sex, BMI and age group 1

	B	SE[a]	*P*	OR	95%	CIs
Sex	-1.714	0.210	<0.01	0.180	0.119	0.272
BMI	-0.152	0.028	<0.01	0.859	0.813	0.907
Age group1[b]	1.082	0.198	<0.01	2.952	2.002	4.351
Constant	4.473	0.777	<0.01	87.589		

a. SE=standard error, b. Age group1: The subjects were divided into two age subgroup: age ⩽60 yrs and age >60 yrs.

Table 6 Logistic regression analysis of sex, BMI and age group 2

	B	SE[a]	*P*	OR	95%	CIs
Sex	-1.668	0.214	<0.01	0.189	0.124	0.287
BMI	-0.156	0.029	<0.01	0.856	0.809	0.905
Age group2[b]	0.609	0.090	<0.01	1.838	1.541	2.193
Constant	4.105	0.790	<0.01	60.662		

a. SE=standard error, b. Age group 2: The subjects were divided into 5 10-year age subgroups (30-39 yrs, 40-49 yrs, 50-59 yrs, 60-69 yrs, 70-79 yrs, *etc.*).

DISCUSSION

Firstly, we wanted to elucidate whether obesity was more prevalent in patients with GCA than in healthy people. After calculating BMI of all the subjects, using the height and weight before the disease for patients who had experienced weight loss before the diagnosis was confirmed, we found that obesity did not tend to be more prevalent in patients with GCA than in healthy control subjects. The mean value of BMI in each group was 22.90 kg/m^2 and 24.85 kg/m^2 (P<0.01). Within each coordinated sex or age subgroup, the patients always had a lower level of BMI (Table 1 and Table 2). The trend did not show any change after sex and age were balanced between the two groups.

We divided all the subjects into four subgroups according to the criteria of BMI for underweight, overweight and obesity proposed by Zhou *et al*[25,26]. After we calculated the relative risk in each group, we found that it did not rise with the elevation of BMI. The ORs for obesity in age groups of 30-59 and 60-79 years were 1.15 (95 % CI=0.37-3.65) and 0.16 (95 % CI=0.05-0.44) for males and 0.78 (95 % CI=0.26-2.36) and 0.28 (95 % CI=0.04-2.05) for females, respectively. On the contrary, underweight people had the greatest risk, ORs for underweight were 2.42 (95 % CI=0.56-10.53) and 4.68 (95 % CI=1.13-19.40) for males in age subgroup 30-59 and 60-79 and 40.7 (95 % CI=9.32-177.92) for females older than 60 yrs. No underweight subject was found in healthy female subjects of 60 yrs old or younger. So the ORs for underweight in this subgroup could not be calculated. After performing Fisher' s exact test, we found that the underweight people were more likely to get GCA (P<0.05) except for men under 60 yrs old (Table 4).

Sex and age might be the influence factors for BMI. Logistic regression was performed to investigate the relationship between BMI and GCA. As shown in Table 5 and Table 6, the association between risk of GCA and BMI was significant (P<0.01). Underweight people showed a high possibility of GCA.

Our results differed greatly from not only those in the Western countries but also those of Chow *et al*. in Shanghai, China[7,8,9,28]. The reasons behind the difference might be the genetic background, life style and cut-off points for BMI. The genetic background of the Chinese people differs greatly from those of the Westerners. It even differs in different parts of China. It has been proved that life styles, including smoking, alcohol consumption, and dietary habits could influence the incidence and prognosis of GCA[29]. Even in China, people in different areas have their particular life styles. For example, citizens of Shanghai take more fresh fruits and vegetables than residents of Beijing. Results of the correlative researches conducted in Shanghai were similar to those of the Westerners. The patients enrolled in our research were mainly from North China, which may cause the difference. Secondly, the cut-off points for underweight, overweight and obesity used in our study were different from those used in previous researches. Our study suggests that obesity should not be a risk factor for the North Chinese people.

According to Siewert' s classification, GCA is classified into three types based on its anatomy location. Yasuhiro *et al* noticed a striking difference between the East and the West in the proportion of patients who fell into each type of GCA[30]. Type I cancer, or adenocarcinoma of the lower esophagus was reported to be more prevalent in the Western countries[31] while type III cancer, or adenocarcinoma of the proximal stomach was predominant in Japan. By reviewing pathologic materials of GCA patients, we found that the distribution of GCA types in our patient group was very similar to that of Japanese (data not shown). Obesity might be a risk factor for type I cancer. GCA might have a particular mechanism in the Eastern countries[32].

GCA tended to be more prevalent in aged people[33]. In our study, the median age of the patient group was significantly higher than that of the control group. Epidemiological evidences showed that the proportion of obese people rose with increase of age. It must be clarified that whether a high proportion of aged people can lead to a high prevalence of obesity in the patients group or obesity really predisposes to GCA. Evidences that were opposed to the reflux theory have been also available[34,35]. Besides, one important precondition of the obesity-reflux-carcinogenesis theory is that reflux is the real risk factor. Our next research will be focused on how reflux influences cells at the gastric cardia.

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