

# Risk factors for the gastric cardia cancer: a case-control study in Fujian Province

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## Abstract

**AIM:** The incidence of gastric cardia cancer has greatly increased in the past 2-3 decades, however, the risk factors for the disease are still not clearly understood. The investigations among Chinese population on the risk factors of gastric cardia cancer were also scarcely reported. We therefore conducted a case-control study in Fujian province, China, to investigate the potential risk and protective factors of this disease.

**METHODS:** 191 cardia and 190 non-cardia gastric cancer cases, and a total of 222 control cases were included in this study. Standard questionnaires were used in collecting epidemiological factors and the data were then analyzed by the unconditional logistic regression model.

**RESULTS:** As the factors such as age, gender, smoking, alcohol consumption, and family history of gastric cancer were controlled, a multivariable analysis was conducted, which revealed that there was a significant correlation between the dietary habits such as irregular meal, over and fast eating, and the gastric cardia cancer with the odds ratios (ORs) of 4.2 (95 % confidence interval: 2.3-7.7), 4.7 (2.1-10.8), and 2.7 (1.3-5.3) respectively. Other correlations were also observed between the gastric cardia cancer and the consumption of salty fish or pickled vegetable, smoking, and the family cancer history with the ORs of 5.5 (1.4-19.5), 1.8 (1.0-3.0), 2.1 (1.3-3.5), and 3.8 (2.3-6.2) respectively. In contrast, the negative correlations were found existing between the intake of fresh vegetables and fruits, the use of refrigerator, and the gastric cardia cancer, with the ORs of 0.4 (0.2-0.9), 0.2 (0.1-0.5), and 0.2 (0.1-0.4), respectively. However, dietary habits were associated less with non-cardia gastric cancer compared with its cardia counterpart.

**CONCLUSION:** Dietary habits might be one of the risk factors for the cardia carcinogenesis among Chinese population.

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## INTRODUCTION

While the total incidence and mortality of gastric cancer manifested a declining trend world wide, the incidence of gastric cardia cancer has increased considerably in the past few decades<sup>[1-4]</sup>. The explanations for this phenomenon, however, have not been fully elucidated yet<sup>[5-6]</sup>. Although certain dietary factors have been suggested to be associated with the gastric carcinogenesis, there are few investigations performing the etiological analysis further on the anatomical sub-site of the cancer<sup>[7-11]</sup>, whose divergent carcinogenesis patterns suggested that there might exist differences in etiological factors between the cardia and non-cardia gastric cancers. To verify this hypothesis, we have conducted a case-control study in Fujian Province, China.

## MATERIALS AND METHODS

### Subjects

191 cardia and 190 non-cardia primary gastric cancer cases, which were pathologically confirmed or diagnosed through surgical operation between April 2000 and June 2001 in six hospitals in Fuzhou, were employed as the observation group and the cancer controls respectively. The 222 cases of normal control, which came from the department of orthopedics in the same hospitals, were selected without cancers or gastric diseases and frequency-matched to the observation cases by age ( $\pm 3$  year) and gender. All subjects in our study must have resided in Fujian Province for more than 20 years and can answer questions clearly.

### Investigation

Face-to-face interviews were conducted in the hospitals by trained interviewers, in which a structured questionnaire containing socio-demographic characteristics, personal medical history, tobacco and alcohol consumption habits, family cancer history, dietary history and dietary habits was used. As for the dietary habits, the exposure time of 10 years before the interview was emphasized to ensure the assessment of potential risk factors with a reasonable latent period before the onset of cancer. Although the dietary habits could be changed presently by the course of the disease, they would never be influenced 10 years earlier. With the agreement to be interviewed, the observed case and his or her control counterparts were investigated by the same interviewer.

### Statistical analysis

The data were statistically evaluated with Epi-info by the univariate and multivariate analysis. The relationship between the putative risk factors and the sub-sites of gastric cancer was assessed by odds ratios (ORs) and their 95 % confidence intervals (CIs) derived from unconditional logistic regression model. Multivariate logistic regression analysis was used to evaluate simultaneously the effects of multiple factors and other potential confounding factors.

## RESULTS

A total of 603 subjects from 30 to 79 years old were included

in this study. In the observation group, there were 156 male and 35 female with the average age of 61.2 ( $\pm 9.7$ ) and 57.3 ( $\pm 10.9$ ) years old respectively. Table 1 shows the demographic characteristics of age and gender for the observed cases and controls. To minimize the possible confounding effects on the investigation results, the age and the gender were taken as the confounding factors to be controlled in all of our analyses.

The relationship between the dietary habits and gastric cancers are shown in Table 2 with the factors such as age, gender, smoking, alcohol consumption and family cancer history being controlled. Irregular meal, over and fast eating could increase the risk of cardia carcinogenesis. Intake of salty fish, pickled vegetables, lard oil and drinking of the well water were also the risk factors for the cardia cancer. In contrast, the intake of fresh vegetables and fruits and the use of refrigerator were belong to the protective factors against the cancer. Besides, it was found that low income, poor education and bearing a family cancer history in the first-degree relatives were associated with the cardia cancer risk. However, the dietary habits

were associated less with non-cardia cancer compared with its cardia counterpart. Alcohol consumption was not observed relating to the cardia cancer risk in the present study.

Table 3 shows the interrelation between cardia cancer and smoking. In smokers, the odds ratio for cardia cancer is 2.09 after adjusted by age, gender, alcohol drinking and family cancer history. For those who smoke more than 20 cigarettes a day, the risk for cardia cancer was 2-fold or more compared with non-smokers. We also noted a significant dose-risk relationship existed between the daily consumed cigarettes, smoking duration and the cardia cancer. However, it was not existed between smoking and the non-cardia gastric cancer.

Unconditional logistic analyses were made by a backward elimination approach to select a possible best subset of risk factors for cardia cancer. The results showed that the best subset of risk factors included family cancer history, irregular meal, fast eating, well-water drinking, smoking, and poor-educated. Fresh fruit intake and the use of refrigerator have protective effect against cardia cancer.

**Table 1** Age and sex distribution of the observed cases and the controls

	Age (yrs)	Controls		Cardia cancer		Gastric cancer		Total		P value
		n	(%)	n	(%)	n	(%)	n	(%)	
Female	30 -	13	(22.8)	2	(5.7)	9	(15.8)	24	(16.1)	0.209
	45 -	15	(26.3)	15	(42.9)	13	(22.8)	43	(28.9)	
	55 -	13	(22.8)	9	(25.7)	19	(33.3)	41	(27.5)	
	65 -	16	(28.1)	9	(25.7)	16	(28.1)	41	(27.5)	
Male	30 -	29	(17.6)	10	(6.4)	17	(12.8)	56	(12.3)	0.025
	45 -	37	(22.4)	27	(17.3)	31	(23.3)	95	(20.9)	
	55 -	44	(26.7)	49	(31.4)	42	(31.6)	135	(29.7)	
	65 -	55	(33.3)	70	(44.9)	43	(32.3)	168	(37.0)	

**Table 3** The interrelation between smoking and kinds of gastric cancers

Variables	Controls		Cardia cancer				Non-cardia gastric cancer			
	n		n	OR*	95%CI	P	n	OR*	95%CI	P
Smoking										
No	120		74				99			
Yes	102		117	2.090	1.261-3.464	0.004	91	1.325	0.814-2.157	0.257
Daily consumed cigarettes										
0	120		74				99			
< 19	37		28	1.443	0.753-2.766	0.270	27	1.092	0.579-2.062	0.785
$\geq 20$	65		89	2.513	1.455-4.339	0.001	64	1.478	0.863-2.531	0.155
P For trend				0.000				0.472		
Smoking duration (yrs)										
0	120		74				99			
< 30	53		37	1.408	0.755-2.625	0.282	36	1.073	0.596-1.933	0.814
$\geq 30$	49		80	2.717	1.548-4.768	0.000	55	1.600	0.906-2.825	0.105
P For trend				0.000				0.289		

\*Adjusted by age, gender, drinking and family cancer history in the first-degree relatives

**Table 4** Multivariate logistic regression analysis

Selected variable	$\beta$	$S\chi$	OR	95% CI	P
Family cancer history	1.455	0.289	4.286	2.431-7.554	0.000
Irregular meal	0.647	0.160	1.909	1.396-2.610	0.000
Fast eating	0.707	0.185	2.028	1.412-2.912	0.000
Fresh fruit intake	-0.439	0.195	0.645	0.439-0.945	0.025
Well-water drinking	0.555	0.262	1.741	1.042-2.910	0.034
Use of refrigerator	-0.313	0.158	0.731	0.536-0.997	0.048
Daily cig. consumption	0.298	0.158	1.347	0.989-1.835	0.059
Years of education	-0.759	0.269	0.468	0.276-0.794	0.005

**Table 2** Potential risk or protective factors for cardia and non- cardia gastric cancers, odds ratios & 95 % confidence Interval (CI)

Variables	Controls		Cardia cancer			Non-cardia gastric cancer			
	<i>n</i>	<i>n</i>	<i>OR*</i>	<i>95%CI</i>	<i>P</i>	<i>n</i>	<i>OR*</i>	<i>95%CI</i>	<i>P</i>
Irregular meals									
No	165	101				98			
Sometimes	36	45	1.971	1.152-3.374	0.013	50	2.310	1.375-3.897	0.002
Frequently	21	45	4.184	2.260-7.747	0.000	42	3.662	1.997-6.717	0.000
<i>P</i> For trend			0.000				0.000		
Over eating for each meal									
No	105	103				156			
Sometimes	55	58	1.864	1.139-3.050	0.013	63	1.806	1.122-1.908	0.015
Frequently	11	28	4.720	2.067-10.781	0.000	24	3.499	1.569-7.801	0.002
<i>P</i> For trend			0.034				0.000		
Eating speed									
Slow	33	18				20			
Moderate	110	67	1.058	0.531-2.107	0.874	85	1.308	0.688-2.485	0.412
Fast	79	106	2.645	1.318-5.307	0.006	85	1.878	0.968-3.644	0.063
<i>P</i> For trend			0.000				0.043		
Years of education									
≤ 6	90	121				96			
> 6	132	70	0.317	0.204-0.492	0.000	94	0.643	0.426-0.972	0.036
Monthly Food Expense (RMB)									
<80	62	79				65			
80-	61	60	0.653	0.387-1.102	0.110	64	0.971	0.580-1.625	0.911
100-	59	34	0.397	0.223-0.710	0.002	46	0.697	0.405-1.199	0.192
200-	40	18	0.313	0.155-0.630	0.001	15	0.356	0.175-0.726	0.004
<i>P</i> For trend			0.000				0.044		
Salty fish intake									
< 1 times/M	170	139				134			
< 3 times/W	49	41	1.019	0.615-1.690	0.941	41	1.058	0.646-1.730	0.824
≥ 3 times/W	3	11	5.518	1.367-19.461	0.015	15	5.706	1.588-20.49	0.008
<i>P</i> For trend			0.111				0.020		
Fresh vegetables intake									
< 3 times/W	14	25				18			
≥ 3 times/W	208	166	0.439	0.212-0.909	0.027	172	0.644	0.303-1.367	0.252
Fresh fruit intake									
< 1 times/M	30	52				44			
< 3 times/W	127	116	0.565	0.328-0.973	0.040	115	0.586	0.339-1.015	0.057
≥ 3 times/W	65	23	0.225	0.112-0.452	0.000	31	0.289	0.149-0.561	0.000
<i>P</i> For trend			0.000				0.000		
Pickled vegetables intake									
< 1 times/M	88	61				69			
< 3 times/W	76	63	1.335	0.804-2.214	0.264	64	1.139	0.701-1.852	0.598
≥ 3 times/W	58	67	1.762	1.044-2.974	0.034	57	1.269	0.766-2.103	0.355
<i>P</i> For trend			0.038				0.367		
Cooking oil									
Other type	56	32				28			
Peanut oil	149	103	0.533	0.347-0.820	0.004	115	0.738	0.485-1.124	0.157
Lard oil	93	117	2.327	1.521-3.562	0.000	107	1.853	1.230-2.794	0.003
Drinking water									
Other type	27	30				32			
Well water	60	98	2.822	1.826-4.360	0.000	76	1.804	1.176-2.768	0.007
Tap water	135	63	0.301	0.195-0.464	0.000	82	0.461	0.306-0.694	0.000
Use of refrigerator									
No	83	108				86			
< 10 yrs	45	46	0.764	0.449-1.302	0.323	53	1.155	0.689-1.935	0.585
≥ 10 yrs	94	37	0.242	0.143-0.409	0.000	51	0.426	0.263-0.693	0.001
<i>P</i> For trend			0.000				0.007		
Family Cancer History									
No	190	122				131			
Yes	32	69	2.090	1.261-3.464	0.004	59	1.325	0.814-2.157	0.257

\*Adjusted by age, gender, smoking, drinking, and family cancer history in the first-degree relatives

## DISCUSSION

Epidemiological studies have indicated that while the overall incidence of gastric cancer has been decreasing, the morbidity of cardia gastric cancer has constantly gone up, which might reflect a different etiology for the cardia gastric cancer<sup>[12-14]</sup>. However, little attention has been paid to the risk factors for this increasing trend of cardia gastric cancer. The correlation between the risk factors and the location of gastric cancer has also seldom been investigated<sup>[15-17]</sup>.

In our study the dietary habits were identified as the risk factors for cardia cancer. Irregular meal, over-eating, and the fast eating may cause injuries to the digestive tract mucosa and promote the carcinogenesis. The protective effects of taking in fresh vegetables and fruits against gastric cancer may be mediated by anti-oxidants such as ascorbic acid. Therefore, intake of more fresh fruits and vegetables may significantly lower the risk of gastric cancer, which is consistent with the former epidemiological studies<sup>[18-21]</sup>. The present study also showed that the more the pickled vegetables and salty fish were taken in, the more the risk for cardia cancer were increasing, which might be attributed to the potential carcinogens, such as nitroso compounds contained in these foods, and may also involved the increased cell replication and susceptibility to carcinogenesis from salt intake<sup>[22-24]</sup>. Lard oil intake was also associated with the increased risk of gastric ca cancer, probably because of excessive exposures of people to the saturated fatty acids. We found that in comparison of the cardia with non-cardia cancer, the carcinogenic risk with specific food or food groups were similar; however, the dietary habits associated more closely with the cardia cancer than with the other stomach carcinomas.

Long-term use of refrigerators could decrease the risk of both cardia and non-cardia gastric cancer with the adjusted OR of 0.242 (95 % CI: 0.143-0.409) and 0.426 (95 % CI: 0.263-0.693) respectively. Refrigerator may keep foods and vegetables fresh for longer period of time, reduce the possibility of generating nitroso compounds, and maintain vitamins and other antioxidants at a higher level, which in turn protect the individuals from exposure to nitroso compounds and other carcinogens. Effective food preservation, which slows down the conversion of nitrates ions to highly carcinogenic nitrites, has been suggested to be at least partially responsible for the overall decreasing trend of gastric cancer incidence.

Well-water, especially shallow well-water may be more easily polluted than tap water. In this study, the fact that well-water drinking was related to an increased risk of cardia cancer suggested that potentially detrimental materials in polluted drinking water might be involved in the cardia carcinogenesis.

After adjusted by age, gender, drinking water and family cancer history in the first-degree relatives, cigarette smoking manifested as a risk factor for the cardia cancer in this study. There was a longer smoking exposure history in the cardia cancer cases than in both cancer-free controls and non-cardia gastric cancer patients. Significant positive dose-effect relationship was found both in the daily cigarette consumption ( $P < 0.001$ ) and the smoking duration ( $P < 0.001$ ). These findings suggested that the smoking exposure was a specific risk factor for the cardia cancer, and the results were influenced less by the recall bias, as it is implausible that patients with cardia cancer would recall smoking exposure more accurately than the non-cardia gastric cancer cases. It is also impossible for the cardia cancer patients to think the more about smoking as the possible cause of their illness than the non-cardia gastric cancer patients, even though cancer cases were aware of their disease status. Therefore, taking multiple controls of different types can be valuable for exploring alternate hypotheses and for taking into account possible potential bias such as recall bias<sup>[25]</sup>.

Low socio-economic status and poor education were also related to the gastric cancer risk<sup>[26]</sup>. The cancer-free controls tended to be better educated than the cancer cases in this study. Family aggregation of the cardia gastric cancer has been confirmed in this study with adjusted OR of 2.09. The correlation between the cardia gastric cancer and family cancer history in the first-degree relatives suggested that inherited genetic susceptibility and shared environmental risk factors might contribute to the cardia carcinogenesis<sup>[27, 28]</sup>.

In conclusion, our study indicated that dietary habits and family cancer history are the risk factors both for cardia and non-cardia gastric cancer. However, dietary habits and smoking were associated more with the cardia cancer than the non-cardia carcinomas. The different epidemiological features between the cardia and the non-cardia gastric cancer suggested that these tumors might have different etiologic profiles. Therefore, further studies on environmental and host determinants of gastric cardia cancer are needed. Our study also suggested that interventions against cigarette smoking and bad dietary habits may be important for the prevention of gastric cancer. As part of the strategy for the cancer control, healthy lifestyle should be emphasized as every one's responsibility<sup>[29, 30]</sup>. Daily intake of fresh vegetables and fruits should be encouraged<sup>[31-33]</sup>.

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