Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.5472

World J Gastroenterol 2009 November 21; 15(43): 5472-5480
World Journal of Gastroenterology ISSN 1007-9327

BRIEF ARTICLE

Etiologic factors of gastric cardiac adenocarcinoma among men in Taiwan

Mei-Ju Chen, Deng-Chyang Wu, Jia-Ming Lin, Ming-Tsang Wu, Fung-Chang Sung

Mei-Ju Chen, Jia-Ming Lin, Fung-Chang Sung, Institute of Environmental Health, National Taiwan University College of Public Health, 17 Xuzhou Road, Zhongzheng District, Taipei City 100, Taiwan, China
Mei-Ju Chen, Department of Nursing, Chung Hwa University of Medical Technology, 89 Wen-Hwa 1st Street, Jen-Te Hsiang, Tainan Hsien 717, Taiwan, China
Deng-Chyang Wu, Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100 Tz-You 1st Road, Kaohsiung City 807, Taiwan, China; Faculty of Medicine, College of Medicine, Kaohsiung Medical University, 100 Shih-Chuan 1st Road, Kaohsiung City 807, Taiwan, China; Research of Excellence for Environmental Medicine, Kaohsiung Medical University, 100 Shih-Chuan 1st Road, Kaohsiung City 807, Taiwan, China
Ming-Tsang Wu, Department of Family Medicine, and Graduate Institute of Occupational Safety and Health, Kaohsiung Medical University Hospital, 100 Tz-You 1st Road, Kaohsiung City 807, Taiwan, China
Fung-Chang Sung, Institute of Environmental Health, China Medical University, College of Public Health, 91 Hsueh-Shih Road, Taichung 404, Taiwan, China
Author contributions: Chen MJ and Sung FC contributed equally to this work; Chen MJ, Lin JM, and Sung FC designed the research; Chen MJ, Wu DC and Wu MT provided data and performed the research; Chen MJ, Lin JM and Sung FC carried out the analysis and interpretation of data; Chen MJ and Sung FC wrote the manuscript.
Supported by China Medical University, Republic of China for Project Grant (CMU-EM01 and CMU94-074)
Correspondence to: Dr. Fung-Chang Sung, Institute of Environmental Health, China Medical University, 91, Hsueh Shih Road, Taichung 404, Taiwan, China. fcsung@mail.cmu.edu.tw
Telephone: +886-4-22035740 Fax: +886-4-22019901
Received: July 30, 2009 Revised: September 10, 2009
Accepted: September 17, 2009
Published online: November 21, 2009

Abstract

AIM: To elucidate etiologic associations between *Helicobacter pylori* (*H pylori*), lifestyle, environmental factors and gastric cardiac adenocarcinoma (GCA) among men.

METHODS: A hospital-based case-control study was conducted in Taiwan from 2000 to 2009. All cases were newly confirmed as primary GCA. Five controls were selected matching with age, sex, and admission date to each case. Participants were informed of potential risk factors with a structured questionnaire by trained interviewers during hospitalization and provided a blood sample for the determination of *H pylori* infection. Odds ratio (OR) and 95% confidence interval (95% CI) were used to evaluate risk, and a multivariate conditional logistic regression model was performed.

RESULTS: All participants recruited for this study were men, consisting of 41 cases and 205 controls. Results of the univariate analysis showed that significant factors associated with the etiology of GCA included *H pylori* (OR = 2.69, 95% CI = 1.30-5.53), cigarette smoking (OR = 2.28, 95% CI = 1.05-4.96), working or exercising after meals (OR = 3.26, 95% CI = 1.31-8.11), salted food (OR = 2.51, 95%CI = 1.08-6.11), fresh vegetables (OR = 0.28, 95% CI = 0.09-0.80), fruits (OR = 0.19, 95% CI = 0.04-0.89), and rice as principal food (OR = 0.53, 95% CI = 0.30-0.85). Multivariate conditional logistic regression models indicated that a significantly elevated risk of contracting GCA was associated with working or exercising after meals (OR = 3.18, 95% CI = 1.23-9.36) and *H pylori* infection (OR = 2.93, 95% CI = 1.42-6.01). In contrast, the consumption of fresh vegetables (OR = 0.22, 95% CI = 0.06-0.83), fruits (OR = 0.28, 95% CI = 0.09-0.79) and rice as principal food (OR = 0.48, 95% CI = 0.24-0.93) remained as significant beneficial factor associated with GCA.

CONCLUSION: Working or exercising after meals and *H pylori* infection increase the risk of GCA, but higher intakes of rice, fresh vegetables and fruits reduce the risk.

Key words: Gastric cardiac adenocarcinoma; *Helicobacter pylori*; Diet; Obesity; Gastroesophageal reflux disease; Cigarette smoking; Family history

Peer reviewers: Toru Ishikawa, MD, Department of Gastroenterology, Saiseikai Niigata Second Hospital, Teraji 280-7, Niigata, Niigata 950-1104, Japan; Dr. Limas Kupcinskas, Professor, Gastroenterology of Kaunas University of Medicine, Mickeviciaus 9, Kaunas LT 44307, Lithuania

Chen MJ, Wu DC, Lin JM, Wu MT, Sung FC. Etiologic factors of gastric cardiac adenocarcinoma among men in Taiwan. *World J Gastroenterol* 2009; 15(43): 5472-5480 Available from:

URL: http://www.wjgnet.com/1007-9327/15/5472.asp DOI: http://dx.doi.org/10.3748/wjg.15.5472

INTRODUCTION

The gastric cardiac adenocarcinoma (GCA) has attracted considerable attention recently as a consequence of the rapid increase in incidence, while the overall rate of gastric cancer has markedly declined in Western countries. Recent studies in China have also shown a statistically significant increasing trend of the disease in the last 16 years[1]. Another striking feature is the strong male predominance (the sex ratio being 6:1) among the patients[2]. However, no established risk factors can explain the male predominance. Previous studies evaluating the etiology of the GCA generally merged with data of both genders, which would distort the findings and dilute any associations. As the reasons for these variations of incidence remain uncertain, there emerged a critical need for epidemiological studies to identify risk factors in male as well as risk factors that might account for the rapid increases in incidence, although it is very rare.

Recent investigations suggest that obesity[3-5] and gastroesophageal reflux disease (GERD)[6] are important risk factors for GCA among the Western population[5]. A Swedish study found that GCA was related to GERD with an odds ratio of 2.3 (OR = 2.3, 95% CI: 1.2-4.3)[6]. Cigarette smoking is also a risk factor[7], but with a lesser degree of strength for GCA[5]. Dietary factors are also thought to play an important role in the GCA etiology. Fresh vegetables and fruits have been inversely associated with GCA in several studies[7]. Diets high in cholesterol, animal protein and vitamin B12 increase the risk[8], whereas several nutrients, particularly those found in plant food (fiber, ascorbic acid and carotenoids), are associated with a reduced risk of GCA[5,8]. Additionally, the use of supplemental calcium/Tums resulted in a significant risk of GCA in a US study[8].

The other main candidate risk factor is the infection with *Helicobacter pylori* (*H pylori*). Evidences have shown that this infection increases the GCA risk in China and other East-Asian population[9-11], but not in the Western population[12,13]. A US population-based case-control study even reported an inverse relationship between Cag$^+$A strains (cytotoxin associated gene A positive strains) of *H pylori* and GCA[14]. The correlation between the GCA and cancer history in first-degree relatives suggests that inherited genetic susceptibility and shared environmental risk factors might contribute to cardiac carcinogenesis[15]. Great differences exist in lifestyles, diet habits and environment between Chinese and the Westerners. The features of Taiwanese lifestyle share many similarities with both the Chinese and the Westerners. Especially, some popular customs and traditions in Taiwanese are much alike to the Chinese. It would be interesting to know whether people in Taiwan share the risk factors of GCA similar to people in mainland China or in Western countries. We conducted the present study to gain a better clue in the etiologic factors shared by lifestyles, diet, and other environmental exposures associated with GCA among men in Taiwan. We additionally investigated the association with *H pylori* infection.

MATERIALS AND METHODS

Study design

A hospital-based case-control study of matched pairs was derived from 2000 to 2009 in Kaohsiung City, Taiwan, to explore the risk factors of GCA associated with lifestyles, dietary habits, *H pylori* infection and other environmental exposure factors.

Data sources

All subjects in our study were drawn from the Kaohsiung Medical University Chung-Ho Memorial Hospital, which has been accredited as a top-grade teaching hospital in southern Taiwan, and used by patients from all socioeconomic categories.

Patients were diagnosed with a primary histologically confirmed incident case of gastric cancer by pathologist as adenocarcinoma type. The pathologists were not aware of the clinical or endoscopic data. We used endoscopy to measure the distance between the gastroesophageal junction and the upper and the lower borders of the tumor. GCA was identified using an endoscope in a retroflexed position and defined as a tumor, and the majority of the tumors was within 5 mm of the squamocolumnar junction. Gastric cardiac cancers include small cancers located in the cardiac region of the stomach or large tumors located primarily in the cardiac region with slight involvement of the esophagocardiac junction[16]. Patients with non-cardia gastric cancer were excluded. Of the 52 cases of histologically confirmed primary GCA by pathologists and gastroenterologists, ten were women excluded in data analyses. One patient was too ill to participate. Eventually, 41 cases agreed to participate in the study.

For each case identified, 5 controls of matched with sex, age (± 3 years), and admission date (± 2 wk) were recruited from inpatients free of cancer in the Family Medicine Departments at the same hospital, including inpatients who came in for a general health check-up. And, subjects with stomach-related diseases were excluded. Overall, the majority of subjects in the control group were healthy, but some controls were patients with hepatitis B, diabetes mellitus, cataract, and/or benign prostate hypertrophy. Of 209 control subjects invited, 205 agreed to participate in the study.

With consent from subjects, trained professional interviewers performed face-to-face interviews at the hospital using a structured questionnaire. To minimize the variation between interviewers in handling the questionnaire, each interviewer interviewed cases and controls by pairs. We were unable to blind the interviewers to the status of cases or controls, but they were unaware of the study hypothesis and were trained to treat subjects with a similar manner. The structured questionnaire was designed to collect detailed information on sociodemographic characteristics, lifestyles such as cigarette smoking, alcohol drinking, areca quid chewing, and diet, the use of nutritional supplements and medication history, serologic assays, family history, and GERD symptoms.

Obesity was measured by body mass index (BMI), according to the height and weight measured at least 2 years prior to the interview. BMI was calculated as body weight in kilograms dived by the square of body height in meters (kg/m^2). The habits of cigarette smoking, alcohol drinking, and areca quid chewing were quantified from information on the age at the initiating, quantity, frequency, and actual duration of consumption, and the cessation age. For analysis, a smoker was defined as someone who had smoked one cigarette or more per day for more than 1 year. Ex-smokers, ex-drinkers, and ex-chewers were defined as those who had quit the habit for more than 6 mo before being diagnosed with cancer or interviewed. Subjects were asked to report their usual consumption frequency of 15 food items more than 1 year before diagnosis or interviewed. This frequency of dietary history exposure was classified into 7 categories: (1) at least once or more per day, (2) three to six times per week, (3) less than three times per week, (4) at least once to three times per month, (5) less than once per month, (6) less than once per year, and (7) never. In addition to the food frequency questionnaire, we asked several questions about general dietary behaviors thought to be related to the digestive tract effect, such as principal food and whether with middle-intensity working or exercising at less than 30 min after meals.

Subjects were also asked to report whether they ever took any nutritional supplements at least 6 mo or longer, and, if so, the type and the frequency of tablets taken were queried. The use of medications history was also collected, such as aspirin, and non-steroidal anti-inflammatory drugs (NSAID).

A blood sample was obtained from subjects at the time of interview. Serum levels of IgG antibodies to *H pylori* and CagA were determined by antigen-specific ELISA. Subjects were first classified as *H pylori* positive or *H pylori* negative, and those who were *H pylori* positive were then classified as CagA positive or CagA negative. Finally, family history was defined as any first-degree relative self-reported by subjects as having been diagnosed with the gastric cancer or disease. To minimize unreliable information, we verified the reported information by asking the subject's family members for confirmation. GERD symptom was defined as someone presented with recurrent heartburn and regurgitation for more than 1 year before being diagnosed or interviewed. The frequency of GERD symptoms was also collected. A field supervisor inspected each subject's medical history and compared with the collected questionnaires, which were then transferred to coding sheets for analysis.

Statistical analysis

All analyses were performed using STATA 7.0 statistical software. The analysis included χ^2 test for the similarity of demographic factors, and a multivariate technique designed for matched case-control studies. Conditional logistic regression models were used to estimate odds ratio (OR) and 95% confidence interval (95% CI) for the associations between GCA and the covariates of interest. All analyses were performed controlling for age and education level to minimize the possible confounding effects. Sociodemographic characteristics, lifestyle and environmental exposure variables were categorized and compared between cases and controls to identify significant variables associated with GCA. We used the matched case-control data estimating in univariate and multivariate analyses of the relations among exposure factors, potential confounding variables, and cancer risk. The multivariate analysis was performed with no interaction terms to identify factors with the greatest impact on the fit of the model predicting the risk of GCA, taking into account other related exposure factors and covariates.

Table 1 Demographic characteristics in GCA patients compared with matched hospital-based controls in a Taiwan case-control study, 2000-2009

Variables	Case	Control	OR[2]	95% CI
Age				
≥ 60 yr	28	132	1.03	0.57-1.96
< 60 yr	13	73	1.00	
Marital status				
Married	35	159	1.63	0.45-5.87
Other	6	46	1.00	
Ethnicity				
Others[1]	10	45	1.12	0.73-1.69
Chinese Taiwanese	31	160	1.00	
Years of schooling				
≤ 9 yr	27	115	2.96	0.65-13.69
> 9 yr	14	90	1.00	
Occupation				
Farmer	16	59	2.14	0.89-5.12
Business	6	22	1.92	0.73-5.06
Industry	9	52	1.36	0.41-4.38
White-collar	10	72	1.00	
Blood type				
Non- A type	32	150	1.03	0.50-2.11
A type	9	55	1.00	
Blood type				
Non-O type	19	114	0.83	0.32-1.96
O type	22	91	1.00	
Economics				
Poor	21	69	2.11	0.81-5.69
Not-poor	20	136	1.00	

[1]Others: Including Native, Chinese, and Hakka. GCA: Gastric cardiac adenocarcinoma; [2]OR: Odds ratio.

RESULTS

Demographic characteristics

To increase the study sensitivity of this male predominant disease, we confirmed 41 GCA male patients and enrolled 205 healthy male controls. Cases were older than controls, but not significant (average age: 64.53 ± 2.17 years *vs* 63.27 ± 1.73 years, $P = 0.28$). BMI and other demographic characteristics were also comparable between these two groups (Table 1).

Table 2 Association between suspected risk factors and risk of gastric cardiac adenocarcinoma in a Taiwan case-control study, 2000-2009

Variables	Case	Control	OR[1]	95% CI
BMI[2] (kg/m^2)				
> 24	11	96	0.89	0.56-1.38
≤ 24	30	109	1.00	
Cigarette smoking				
Yes	29	110	2.28[a]	1.05-4.96
No	12	95	1.00	
Alcohol consumption				
Yes	18	65	1.71	0.88-3.26
No	23	140	1.00	
Areca quid chewing				
Yes	9	20	2.75	0.86-8.77
No	32	185	1.00	
Daily exercise				
Yes	10	83	0.58	0.16-2.16
No	31	122	1.00	
Sleep with others in childhood				
Yes	37	165	2.10	0.44-10.24
No	4	40	1.00	
Working or exercising after meals				
Yes	27	74	3.26[a]	1.31-8.11
No	14	131	1.00	
H pylori serum				
Positive	30	118	2.69[a]	1.30-5.53
Negative	11	87	1.00	
Cag$^+$A[3]				
Positive	27	102	1.27	0.21-7.66
Negative	3	16	1.00	
GERD symptoms				
Yes	11	48	1.28	0.64-2.55
No	30	157	1.00	
Passive smoking (family)				
Yes	17	66	1.48	0.37-5.92
No	24	139	1.00	
Passive smoking (colleague)				
Yes	18	91	1.01	0.37-2.59
No	23	114	1.00	
Steaming hot dietary habits (/d)				
Yes	31	175	0.72	0.32-1.53
No	10	30	1.00	
Cold dietary habits (/d)				
Yes	12	62	0.94	0.32-2.75
No	29	143	1.00	
Water supply				
Non-tap-water	13	53	1.47	0.29-7.31
Tap-water	28	152	1.00	

[1]Odds ratio (OR): Adjusted by age and years of schooling; [2]BMI: Obesity: BMI more than 28 kg/m^2; Overweight: BMI more than 24 and less than 28 kg/m^2; Normal: BMI more than 18.5 and less than 24 kg/m^2; Underweight: BMI less than 18.5 kg/m^2; [3]Cag$^+$A: Cytotoxin associated gene A positive strains. (Those who were *H pylori* positive were classified by CagA strains). [a]P < 0.05.

Table 3 Association between suspected dietary pattern and risk of gastric cardiac adenocarcinoma in a Taiwan case-control study, 2000-2009

Variables	Case	Control	OR[1]	95% CI
Nitrate food (times/wk)				
≥ 3	9	23	2.18	0.80-5.89
< 3	32	182	1.00	
Smoked food (times/wk)				
≥ 3	8	30	1.94	0.53-7.34
< 3	33	175	1.00	
Fermented beans (times/wk)				
≥ 3	11	24	2.87	0.82-9.77
< 3	30	181	1.00	
Salted food (times/wk)				
≥ 3	9	21	2.51[a]	1.08-6.11
< 3	32	184	1.00	
Pickled vegetables (times/wk)				
≥ 3	8	34	1.20	0.41-3.36
< 3	33	171	1.00	
Biting food (times/wk)				
≥ 3	6	58	0.38	0.08-2.01
< 3	35	147	1.00	
Galic (times/wk)				
≥ 3	10	60	0.62	0.17-2.12
< 3	31	145	1.00	
Dairy products (times/wk)				
≥ 3	7	47	0.72	0.13-4.15
< 3	34	158	1.00	
Meat (servings/d)				
≥ 6	30	150	1.24	0.42-3.67
< 6	11	55	1.00	
Fresh vegetables (servings/d)				
≥ 2	25	184	0.28[a]	0.09-0.80
< 2	16	21	1.00	
Fresh fruits (servings/d)				
≥ 2	15	169	0.19[a]	0.04-0.89
< 2	26	36	1.00	
Stripped sweet potato (sun-dried)				
Yes	20	71	1.71	0.86-3.37
No	21	134	1.00	
Rice as principal food				
Yes	32	176	0.53[a]	0.30-0.85
No	9	29	1.00	
Milk (/d)				
Yes	16	81	1.02	0.16-7.08
No	25	124	1.00	
Coffee preference (/d)				
Yes	13	62	1.20	0.55-2.53
No	28	143	1.00	
Tea (/d)				
Yes	18	110	0.69	0.36-1.29
No	23	95	1.00	

[1]Odds ratio (OR): Adjusted by age and years of schooling. [a]P < 0.05.

Suspected risk factors

Table 2 shows the relationship between lifestyle habits, environmental exposures and GCA controlling for age and years of schooling of participants. The estimated ORs were significantly elevated in persons with cigarette smoking (current smoking plus ex-smoking: OR = 2.28, 95% CI = 1.05-4.96), working or exercising after meals (OR = 3.26, 95% CI = 1.31-8.11) and *H pylori* infection (OR = 2.69, 95% CI = 1.30-5.53). Cases were also more likely than controls to use alcohol and chew areca quit, but difference was not statistically significant compared with that for abstainers. And other environmental exposure factors were not significantly associated.

However, age-and-years of schooling-adjusted OR estimates revealed harmful associations for GCA with salted food (OR = 2.51, 95% CI = 1.08-6.11) (Table 3). In contrast, there were beneficial effects from the consumption of fresh vegetables (OR = 0.28, 95% CI = 0.09-0.80), fruits (OR = 0.19, 95% CI = 0.04-0.89), and rice as principal food (OR = 0.53, 95% CI = 0.30-0.85). We failed to

Table 4 Association between nutritional supplement and risk of gastric cardiac adenocarcinoma in a Taiwan case-control study, 2000-2009

Variables	Case	Control	OR[1]	95% CI
Vitamine				
Yes	6	42	0.63	0.18-1.95
No	35	163	1.00	
Vit A				
Yes	2	13	0.74	0.24-2.50
No	39	192	1.00	
Vit B				
Yes	2	18	0.49	0.07-3.46
No	39	187	1.00	
Vit C				
Yes	3	25	0.56	0.10-3.36
No	38	180	1.00	
Vit E				
Yes	5	23	0.99	0.20-4.81
No	36	182	1.00	
Vit B complex				
Yes	4	14	1.59	0.74-3.43
No	37	191	1.00	
Iron				
Yes	3	6	2.01	0.86-4.68
No	38	199	1.00	
Calcium tablet				
Yes	4	26	0.84	0.17-4.12
No	37	179	1.00	
Zinc tablet				
Yes	1	6	0.85	0.09-8.10
No	40	199	1.00	
Aspirin				
Yes	2	7	1.34	0.59-3.03
No	39	198	1.00	
NSAID				
Yes	4	14	1.29	0.47-3.71
No	37	191	1.00	

[1]Odds ratio (OR): Adjusted by age and years of schooling.

find significant associations between GCA and vitamin supplements and other supplements or medications such as iron, calcium tablet, zinc tablet, aspirin, and NSAID (Table 4).

The risk strength associated with family disease history is shown by adjusted OR in Table 5. To investigate the actual effects of family aggregation, we collected relevant information about patient's first-degree relatives. There were insignificant weak evidences to associate GCA risk with family anemia history and other forms of gastric disease as well as atrophy gastritis, gastric ulcer, lymphoma, gastric polypus, and gastric cancer. However, individuals with a family history of duodenal ulcer (OR = 0.82, 95% CI = 0.35-2.09) had a reduced nonsignificant risk for GCA.

All significant variables found in the univariate analyses were included in the multivariate conditional logistic regression analysis (Table 6). The significantly elevated OR for GCA were associated with working or exercising after meals (OR = 3.18, 95% CI = 1.23-9.36) and *H pylori* infection (OR = 2.93, 95% CI = 1.42-6.01). However, consumption of fresh vegetables (OR = 0.22, 95% CI = 0.06-0.83), fruits (OR = 0.28, 95% CI = 0.09-0.79), and rice as principal food (OR = 0.48, 95% CI = 0.24-0.93) remained as protective factors that reduced the risk of GCA.

Table 5 Association between family history and risk of gastric cardiac adenocarcinoma in a Taiwan case-control study, 2000-2009

Variables	Case	Control	OR[1]	95% CI
Anemia				
Yes	17	83	1.06	0.46-2.58
No	24	122	1.00	
Atrophy gastritis				
Yes	17	85	1.02	0.31-3.25
No	24	120	1.00	
Gastric ulcer				
Yes	15	73	1.23	0.39-3.79
No	26	132	1.00	
Duodenal ulcer				
Yes	16	88	0.82	0.35-2.09
No	25	117	1.00	
Lymphoma				
Yes	12	57	1.30	0.63-2.80
No	29	148	1.00	
Gastric polypus				
Yes	13	62	1.51	0.20-11.38
No	28	143	1.00	
Cancer				
Yes	10	24	2.54	0.83-7.75
No	31	181	1.00	
Sibling (Cancer)				
Yes	5	23	1.39	0.38-5.06
No	36	182	1.00	

[1]Odds ratio (OR): Adjusted by age and years of schooling.

Table 6 Multivariate conditional logistic regression analysis for estimated OR and 95% CI for GCA patients compared with matched hospital-based controls in Taiwan, 2000-2009

Variables	OR[1]	95% CI
H pylori infection	2.93[a]	1.42-6.01
Cigarette smoking	2.26	0.35-15.20
Working or exercising after meals	3.18[a]	1.23-9.36
Consumption of salted food	2.34	0.39-13.75
Consumption of fresh vegetables	0.22[a]	0.06-0.83
Consumption of fresh fruits	0.28[a]	0.09-0.79
Rice as principal food	0.48[a]	0.24-0.93

[1]Odds ratio (OR): Adjusted by age and years of schooling. [a]$P < 0.05$.

DISCUSSION

To our knowledge, this is the first study to explore simultaneously all aspects of factors that may associate with GCA, including *H pylori* infection, lifestyle, dietary and nutritional supplements taking history, and family history.

It took 10 years to identify 41 histologically confirmed primary GCA cases with useful data. But, this small sample size study has demonstrated important findings. The habit of working or exercising after meals was the strongest risk factors for GCA among men in Taiwan, which is consistent with the finding for Chinese population in Fujian Province[7]. One plausible biological explanation for this association is that working or exercising after meals may decrease blood supply in digestive tract and induce gastric ischemia to prolong the empty time[17]. Besides, physical activity may increase the intra-abdominal pressure and wall tension in the digestive tract, and reduced gastric mucosal flow and ischemia[17]. And recent studies have indicated that the cardiac region differs from the rest of the stomach by remaining highly acidic after a meal[18]. Physical activity may thus increase the gastrointestinal transit time and also extend acid contact time between the gastric mucosa, cardiac region especially, and potential carcinogens in the stomach, eventually leading to an increased GCA risk.

Most of the studies from Western populations have found no significant association with *H pylori* in the GCA etiology[12,13]. Some studies even reported a reduced risk for the disease[14,19]. In contrast, most studies conducted in Asian population[9-11,20] have found elevated risks from *H pylori* infection. A meta-analysis of prospective studies, including only four studies, found no association between GCA and *H pylori*[21]. Of these, two studies from China indicated an elevated risk associated with infection while other two from Europe indicated a reduced risk. Clearly, our finding is consistent with observations in Asian studies, encouraging evidence of the harmful role of *H pylori* in the carcinogenic process for GCA. The divergent findings between European and Chinese leave a matter for future consideration.

However, we observed that CagA seropositivity played no significant role consistent with prospective studies from China[11] and Europe[10]. Of interest, CagA seropositivity was associated with a 6.2-fold greater risk for cancers in the upper one third of the stomach for Japanese (1.2-32.0)[12]. In contrast, CagA seropositivity (OR = 0.4, 95% CI = 0.2-0.8) was associated with a reduced GCA risk in the US[14]. The inconsistency of these findings may be due to the diversity of the studies in geography, and ethnicity among them because of important genetic components, host, and environmental heterogeneity.

Furthermore, the CagA antibodies measurement for each subject reduced our misclassification of *H pylori* status. This encourages the power of testing significance with such a small sample size in this study. Therefore, we suggest that *H pylori* measurement in early life is an important marker of GCA, and a future study to elucidate the transmission mechanism of *H pylori* infection for the GCA prevention relevancy is needed.

Salted food has been linked to stomach cancer risk[22-24]. We found that salted food was also associated with an increased risk for GCA. However, this risk disappeared in the multivariate statistical models. Salt is thought to induce an inflammatory process leading to the damage of the protective stomach mucosa. And, *H pylori* may interact with salt and enhances carcinogenesis after the gastric epithelium is damaged[24]. It may also increase cell susceptibility to carcinogenesis from salt intake[7]. Thus, we postulate that salt per se is not an independent carcinogen, as Cohen *et al*[25] argued, but a promoter of GCA.

Many studies have reported the protective effect from the intake of fresh vegetables and fruits against GCA[7,26,27]. We also showed a remarkably reduced risk of GCA for men consuming diet rich with fresh vegetables and fruits. In other words, the plant food was associated with a strong reduction in risk for GCA among men in Taiwan. Plant food is rich in fiber, ascorbic acid and carotenoids[5,8]. Several studies showed that dietary fiber was strongly related to a reduced GCA risk[8,27,28]. The protective mechanism of fiber is still unclear; it may play a cleansing role and could facilitate the removal of carcinogens at the epithelial surface[27] or promote the sloughing of damaged epithelial cells[8]. Ascorbic acid and carotenoids are both strong antioxidants in the process of gastric carcinogenesis. Nevertheless, our data not only confirmed the beneficial effect of fresh vegetables and fruits against GCA, but also suggested rice as the principal food is important against this disease.

This study showed that rice as principal food may well reduce the risk of GCA in Taiwan. Antioxidants and fiber effect in rice, with much lower protein composition than wheat and some other grains, may attribute to the anti-carcinogenicity[29-32]. The decreased protein content in meals may reduce gastric acid secretion[33]. Cardiac cancer in Western countries has been associated with normal or increased acid production[6]. Rice as principal food may lower acid secretion, thus reducing the GCA risk. According to our observation of the habit of working or exercising after meals or rice as principal food, similar to those of the West, we assume that chronic exposure to gastric acid plays a role in the aetiology of GCA. Although we failed to observe an association between GERD and the GCA risk, the result is well in agreement with other studies conducted in the US[31] and Taiwan[34,35]. GERD is less common in Asians than in Western population[34,36]. We, therefore, considered GERD as an indicator rather than a crucial cause of GCA.

Our results differed greatly from the Western studies[3,5] in the association with BMI. Similar to a recent North China study[37], we found a negative association between obesity and GCA, although not significant. The reasons of the difference might be associated with the genetic background, cut-off points for BMI and lifestyle. Great differences exist in lifestyle and diet habits between Chinese and the Westerners. Asian populations historically eat low-fat diets[38] with more vegetables/fruits[39] and have a smaller BMI than Western populations[40]. This suggests that obesity is an indirect factor in the association with GCA for the men in Taiwan. Moreover, a recent China study has pointed out that the westernization in diet and eating habits is responsible for the higher risk of GCA in the urban area than in the rural area[41].

Some studies found harmful effect from smoking for GCA[5,7,42,43]. The present study observed a significant risk associated with smoking, but it disappeared in the multivariate analysis. Thus, it may be attributed to the reinforcing factor but not an independent carcinogen for GCA. Besides, the sample size of GCA cases in this study might be not large enough to detect such a relationship; however, we still can not overlook its gravity.

A twin study assessing the contribution of hereditary and environmental factors has found that occupational exposures and viral infections make up the other 62% of the risk of developing stomach cancer. The statistical model used provided a perfect fit (P = 1.0) in predicting the involvement of major environmental factors plus minor genetic components for the risk of stomach cancer[44]. Our results support this notion, even though we have no direct witness to prove it. In our study, working or exercising after meals, vegetables, fruits and rice consumption and *H pylori* infection are significantly associated with GCA, but not in family history of gastric diseases with the familial (hereditary or nonhereditary) effects. This finding indirectly shows the etiological importance of environmental factors for GCA.

An important etiologic characteristic of GCA is the strong male predominance. This study did find 42 of 52 cases were men. Why did the strong male predominance exist among patients with GCA? As the family is the core unit of *H pylori* transmission[45] and childhood colonization has the same risks in males and females. The striking feature may be due to the fact that females work or exercise at the lower intensity than males, because of the Chinese social request of culture. Hence, males are at higher risk than females for GCA. Moreover, females have more frequent consumption of vegetables and fruits than males. Accordingly, we can find the fact of more protective effect in females than in males. Consequently, the strong male predominance will be continuously observed.

Our study is subject to some limitations. The major limitation is its relatively small sample size, as GCA remains a very rare disease not only worldwide but also in Taiwan[34]. But our stringent matching design has increased the effort in study precision and reduced bias[46]. Compared with published studies[3,19,21], we are encouraged to have more GCA cases with no misclassification and no divergent effects. Another limitation found in this study is the potential for recall bias, a common limitation of case-control studies, as well as the recall bias of dietary and family history. It was not possible to adjust completely for biases such as the dietary recall bias. We did match, however, the time of hospital visits to avoid differences caused by seasonal dietary changes. Moreover, we used the structured questionnaire to collect categorized information to minimize errors in quantitative data caused by incorrect recall. Furthermore, family history data was only collected for first-degree relatives, such self-reported information is generally more reliable. And we did examine and reconfirm family histories by talking with other family members. But, it cannot still wholly excluded that some family histories may have been misclassified.

The advantage of this study was based on confirmed GCA cases validated by a panel of pathologists and gastroenterologists. The other strength in this study is our exact study design and statistical analysis. The high response rate (97.62% in cases and 98.09% in controls), absence of proxy interviews and the homogeneity of control group are the other important ones.

Despite the relatively low number of GCA cases, the main risk factors in Taiwan societies are well established. The epidemiological features of GCA in our study have in deed demonstrated that GCA is more closely governed by environmental factors. Concerning the etiology of GCA, unlike in the West, obesity, GERD and cigarette smoking may not be the independent contributing factors for population in Taiwan. While lifestyle and dietary variables have an important role, infectious origin is still a major factor in the developing populations such as Taiwan. Our further analysis showed an interactive effect between working or exercising after meals and *H pylori* infection. The OR for GCA increased to 3.39 (95% CI 1.32-11.27), compared with individuals of neither working/exercising after meals and nor *H pylori* infection. In conclusion, this study suggests that healthy dietary habits to avoid the chronic exposure to higher and provocative gastric acidity and eradication of *H pylori* are important for the GCA prevention. Daily intake of fresh vegetables, fruits and rice as principal food should be encouraged for the beneficial effect to prevent GCA.

ACKNOWLEDGMENTS

We thank the physicians and nurses in the Departments of Gastroenterology and Family Medicine, Kaohsiung Medical University Chung-Ho Memorial Hospital, for their assistance in this study.

COMMENTS

Background

The gastric cardiac adenocarcinoma (GCA) is a very rare disease. In recent decades, however, the incidence of the GCA has increased dramatically in many Western countries. An increasing trend in GCA is also observed in municipal regions but not in rural regions of China. Another striking feature is the strong male predominance among patients with GCA. Some of the reasons above are still unclear and require further epidemiological investigations.

Research frontiers

The etiological factors associated with this rare disease remain unclear and require a comprehensive investigation in Taiwan. And no corresponding sex difference in the established risk factors for GCA can explain the male predominance. This is the first study which explores simultaneously all potentially factors associating with the disease among men, including *Helicobacter pylori* (*H pylori*) infection, lifestyle, diet and nutritional supplements intake history and family history of the disease in the Chinese population. And, this is the first study to explain the male predominance by sex differences in risk factor profiles of the disease.

Innovations and breakthroughs

This study showed that working or exercising after meals, and *H pylori* infection may increase the risk of GCA. Moreover, the interactive effect between working or exercising after meals and *H pylori* infection augments the risk while rice as principal food and higher intakes of fresh vegetables and fruits may well reduce the risk.

Applications

Avoiding laborious task after meals and diet control may help prevent GCA. Earlier detection and eradication of *H pylori* may refer to the clinical selective direction of prophylaxis and treatment of this disease.

Peer review

This study evaluated retrospectively the risk factors of GCA among men. The results are interesting and suggest that working or exercising after meals and *H pylori* infection are important independent risk factors for GCA, but $Cag^{+}A$ strains of *H pylori* are not associated with this cancer. Furthermore, this study also demonstrates that rice as principal food and consumption of fresh vegetables and fruits may well reduce the risk of GCA.

REFERENCES

1 **He YT**, Hou J, Chen ZF, Qiao CY, Song GH, Meng FS, Jin HX, Chen C. Trends in incidence of esophageal and gastric cardia cancer in high-risk areas in China. *Eur J Cancer Prev* 2008; **17**: 71-76

2 **Parkin DM**. Global cancer statistics in the year 2000. *Lancet Oncol* 2001; **2**: 533-543
3 **MacInnis RJ**, English DR, Hopper JL, Giles GG. Body size and composition and the risk of gastric and oesophageal adenocarcinoma. *Int J Cancer* 2006; **118**: 2628-2631
4 **Lindblad M**, Rodriguez 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**: 285-294
5 **Mayne ST**, Navarro SA. Diet, obesity and reflux in the etiology of adenocarcinomas of the esophagus and gastric cardia in humans. *J Nutr* 2002; **132**: 3467S-3470S
6 **Lagergren J**, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999; **340**: 825-831
7 **Cai L**, Zheng ZL, Zhang ZF. Risk factors for the gastric cardia cancer: a case-control study in Fujian Province. *World J Gastroenterol* 2003; **9**: 214-218
8 **Mayne ST**, Risch HA, Dubrow R, Chow WH, Gammon MD, Vaughan TL, Farrow DC, Schoenberg JB, Stanford JL, Ahsan H, West AB, Rotterdam H, Blot WJ, Fraumeni JF Jr. Nutrient intake and risk of subtypes of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 1055-1062
9 **Kamangar F**, Qiao YL, Blaser MJ, Sun XD, Katki H, Fan JH, Perez-Perez GI, Abnet CC, Zhao P, Mark SD, Taylor PR, Dawsey SM. Helicobacter pylori and oesophageal and gastric cancers in a prospective study in China. *Br J Cancer* 2007; **96**: 172-176
10 **Limburg P**, Qiao Y, Mark S, Wang G, Perez-Perez G, Blaser M, Wu Y, Zou X, Dong Z, Taylor P, Dawsey S. Helicobacter pylori seropositivity and subsite-specific gastric cancer risks in Linxian, China. *J Natl Cancer Inst* 2001; **93**: 226-233
11 **Kikuchi S**, Wada O, Nakajima T, Nishi T, Kobayashi O, Konishi T, Inaba Y. Serum anti-Helicobacter pylori antibody and gastric carcinoma among young adults. Research Group on Prevention of Gastric Carcinoma among Young Adults. *Cancer* 1995; **75**: 2789-2793
12 **Palli D**, Masala G, Del Giudice G, Plebani M, Basso D, Berti D, Numans ME, Ceroti M, Peeters PH, Bueno de Mesquita HB, Buchner FL, Clavel-Chapelon F, Boutron-Ruault MC, Krogh V, Saieva C, Vineis P, Panico S, Tumino R, Nyren O, Siman H, Berglund G, Hallmans G, Sanchez MJ, Larranaga N, Barricarte A, Navarro C, Quiros JR, Key T, Allen N, Bingham S, Khaw KT, Boeing H, Weikert C, Linseisen J, Nagel G, Overvad K, Thomsen RW, Tjonneland A, Olsen A, Trichoupoulou A, Trichopoulos D, Arvaniti A, Pera G, Kaaks R, Jenab M, Ferrari P, Nesi G, Carneiro F, Riboli E, Gonzalez CA. CagA+ Helicobacter pylori infection and gastric cancer risk in the EPIC-EURGAST study. *Int J Cancer* 2007; **120**: 859-867
13 **Ye W**, Held M, Lagergren J, Engstrand L, Blot WJ, McLaughlin JK, Nyren O. Helicobacter pylori infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *J Natl Cancer Inst* 2004; **96**: 388-396
14 **Chow WH**, Blaser MJ, Blot WJ, Gammon MD, Vaughan TL, Risch HA, Perez-Perez GI, Schoenberg JB, Stanford JL, Rotterdam H, West AB, Fraumeni JF Jr. An inverse relation between cagA+ strains of Helicobacter pylori infection and risk of esophageal and gastric cardia adenocarcinoma. *Cancer Res* 1998; **58**: 588-590
15 **Dhillon PK**, Farrow DC, Vaughan TL, Chow WH, Risch HA, Gammon MD, Mayne ST, Stanford JL, Schoenberg JB, Ahsan H, Dubrow R, West AB, Rotterdam H, Blot WJ, Fraumeni JF Jr. Family history of cancer and risk of esophageal and gastric cancers in the United States. *Int J Cancer* 2001; **93**: 148-152
16 **Goldblum JR**, Vicari JJ, Falk GW, Rice TW, Peek RM, Easley K, Richter JE. Inflammation and intestinal metaplasia of the gastric cardia: the role of gastroesophageal reflux and H. pylori infection. *Gastroenterology* 1998; **114**: 633-639
17 **Otte JA**, Oostveen E, Geelkerken RH, Groeneveld AB, Kolkman JJ. Exercise induces gastric ischemia in healthy volunteers: a tonometry study. *J Appl Physiol* 2001; **91**: 866-871
18 **Fletcher J**, Wirz A, Young J, Vallance R, McColl KE. Unbuffered highly acidic gastric juice exists at the gastroesophageal junction after a meal. *Gastroenterology* 2001; **121**: 775-783
19 **Henrik Siman J**, Forsgren A, Berglund G, Floren CH. Helicobacter pylori infection is associated with a decreased risk of developing oesophageal neoplasms. *Helicobacter* 2001; **6**: 310-316
20 **Lin JT**, Wang LY, Wang JT, Wang TH, Yang CS, Chen CJ. A nested case-control study on the association between Helicobacter pylori infection and gastric cancer risk in a cohort of 9775 men in Taiwan. *Anticancer Res* 1995; **15**: 603-606
21 Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001; **49**: 347-353
22 **Tsugane S**. Salt, salted food intake, and risk of gastric cancer: epidemiologic evidence. *Cancer Sci* 2005; **96**: 1-6
23 **Tsugane S**, Sasazuki S, Kobayashi M, Sasaki S. Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. *Br J Cancer* 2004; **90**: 128-134
24 **van den Brandt PA**, Botterweck AA, Goldbohm RA. Salt intake, cured meat consumption, refrigerator use and stomach cancer incidence: a prospective cohort study (Netherlands). *Cancer Causes Control* 2003; **14**: 427-438
25 **Cohen AJ**, Roe FJ. Evaluation of the aetiological role of dietary salt exposure in gastric and other cancers in humans. *Food Chem Toxicol* 1997; **35**: 271-293
26 **Gonzalez CA**, Pera G, Agudo A, Bueno-de-Mesquita HB, Ceroti M, Boeing H, Schulz M, Del Giudice G, Plebani M, Carneiro F, Berrino F, Sacerdote C, Tumino R, Panico S, Berglund G, Siman H, Hallmans G, Stenling R, Martinez C, Dorronsoro M, Barricarte A, Navarro C, Quiros JR, Allen N, Key TJ, Bingham S, Day NE, Linseisen J, Nagel G, Overvad K, Jensen MK, Olsen A, Tjonneland A, Buchner FL, Peeters PH, Numans ME, Clavel-Chapelon F, Boutron-Ruault MC, Roukos D, Trichopoulou A, Psaltopoulou T, Lund E, Casagrande C, Slimani N, Jenab M, Riboli E. Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Int J Cancer* 2006; **118**: 2559-2566
27 **Brown LM**, Swanson CA, Gridley G, Swanson GM, Schoenberg JB, Greenberg RS, Silverman DT, Pottern LM, Hayes RB, Schwartz AG. Adenocarcinoma of the esophagus: role of obesity and diet. *J Natl Cancer Inst* 1995; **87**: 104-109
28 **Wu AH**, Tseng CC, Hankin J, Bernstein L. Fiber intake and risk of adenocarcinomas of the esophagus and stomach. *Cancer Causes Control* 2007; **18**: 713-722
29 **Liao HF**, Chen YY, Yang YC, Wang CS, Chen YJ. Rice (Oryza sativa L.) inhibits growth and induces differentiation of human leukemic U937 cells through activation of peripheral blood mononuclear cells. *Food Chem Toxicol* 2006; **44**: 1724-1729
30 **Johnson IT**. Antioxidants and anticarcinogens. *Eur J Cancer Prev* 1998; **7** Suppl 2: S55-S62
31 **Terry P**, Lagergren J, Ye W, Wolk A, Nyren O. Inverse association between intake of cereal fiber and risk of gastric cardia cancer. *Gastroenterology* 2001; **120**: 387-391
32 **Bienvenido O**, Juliano. The American association of cereal chemists. In: Paul St, editor. Rice: chemistry and technology. 2nd ed. USA, Minneapolis: Minnesota Press, 1985: 8-9
33 **Widmaier EP**, Raff H, Strang KT. Vander's human physiology: the mechanisms of body function. 10th ed. New York: McGraw-Hill international edition, 2006: 595
34 **Chang SS**, Lu CL, Chao JY, Chao Y, Yen SH, Wang SS, Chang FY, Lee SD. Unchanging trend of adenocarcinoma of the esophagus and gastric cardia in Taiwan: a 15-year experience in a single center. *Dig Dis Sci* 2002; **47**: 735-740
35 **Chen MJ**, Wu DC, Ko YC, Chiou YY. Personal history and

family history as a predictor of gastric cardiac adenocarcinoma risk: a case-control study in Taiwan. *Am J Gastroenterol* 2004; **99**: 1250-1257

36 **Goh KL**, Chang CS, Fock KM, Ke M, Park HJ, Lam SK. Gastro-oesophageal reflux disease in Asia. *J Gastroenterol Hepatol* 2000; **15**: 230-238

37 **Zhang J**, Su XQ, Wu XJ, Liu YH, Wang H, Zong XN, Wang Y, Ji JF. Effect of body mass index on adenocarcinoma of gastric cardia. *World J Gastroenterol* 2003; **9**: 2658-2661

38 **Williams GM**, Williams CL, Weisburger JH. Diet and cancer prevention: the fiber first diet. *Toxicol Sci* 1999; **52**: 72-86

39 **California Department of Health Services**. Behavioral risk factor surveillance system. Sacramento: California Department of Health Service, 2002

40 **Deurenberg P**, Yap M, van Staveren WA. Body mass index and percent body fat: a meta analysis among different ethnic groups. *Int J Obes Relat Metab Disord* 1998; **22**: 1164-1171

41 **Fan YJ**, Song X, Li JL, Li XM, Liu B, Wang R, Fan ZM, Wang LD. Esophageal and gastric cardia cancers on 4238 Chinese patients residing in municipal and rural regions: a histopathological comparison during 24-year period. *World J Surg* 2008; **32**: 1980-1988

42 **Tran GD**, Sun XD, Abnet CC, Fan JH, Dawsey SM, Dong ZW, Mark SD, Qiao YL, Taylor PR. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer* 2005; **113**: 456-463

43 **Freedman ND**, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, Schatzkin A. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol* 2007; **165**: 1424-1433

44 **Lichtenstein P**, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000; **343**: 78-85

45 **Niv Y**. Family history of gastric cancer: should we test and treat for Helicobacter pylori? *J Clin Gastroenterol* 2003; **36**: 204-208

46 **Schlesselman JJ**. Case-control studies. Design, Conduct, Analysis. 9th ed. New York: Oxford University Press, Inc., 1982: 105-123

S- Editor Li LF **L- Editor** Ma JY **E- Editor** Ma WH