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• *GASTRIC CANCER* •

Nutritional factors and gastric cancer in Zhoushan Islands, China

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Abstract

AIM: To investigate the association between nutrient intakes and high incidence rate of gastric cancer among residents in Zhoushan Islands.

METHODS: A frequency-matched design of case-control study was used during the survey on dietary factors and gastric cancer in Zhoushan Islands, China. A total of 103 cases of gastric cancer diagnosed in 2001 were included in the study and 133 controls were randomly selected from the residents in Zhoushan Islands. A food frequency questionnaire was specifically designed for the Chinese dietary pattern to collect information on dietary intake. A computerized database of the dietary and other relative information of each participant was completed. Total calories and 15 nutrients were calculated according to the food composition table and their adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by gender using unconditional logistic regression models.

RESULTS: High intakes of protein, saturated fat, and cholesterol were observed with the increased risk of gastric cancer particularly among males ($OR_{Q4\ vs\ Q1}$ were 10.3, 3.24, 2.76 respectively). While carbohydrate was a significant high-risk nutrient ($OR_{Q4\ vs\ Q1}$ = 14.8; *P* for linear trend = 0.024) among females. Regardless of their gender, the cases reported significantly higher daily intake of sodium mainly from salts. As to the nutrients of vitamins A and C, an inversed association with the risk of GC was found. Baseline characteristics of participants were briefly described.

CONCLUSION: The findings from this study confirm the role of diet-related exposure in the etiology of gastric cancer from the point of view of epidemiology. An increased risk of gastric cancer is associated with high intakes of protein, saturated fat, cholesterol and sodium, while consumption of polyunsaturated fat, vitamin A and ascorbic acid may have a protective effect against gastric cancer.

Key words: Gastric cancer; Nutrient intake; Case-control; Risk factor; Protective effect; Antioxidants

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INTRODUCTION

Though a decreasing trend is observed in nearly all countries, gastric cancer is one of the most common cancers in the world and the second leading cause of cancer death[1]. Although many risk factors have been suggested, the causative and protective agents for gastric cancer remain to be clarified. Nutritional factors are thought to be paramount, with *N*-nitroso and other dietary compounds acting as carcinogens, while anti-oxidants and other protective substances in foods inhibit the carcinogenic process[2].

In China, parts of high-risk areas for gastric cancer are located in the eastern coastlands including Zhoushan Islands, the fourth archipelago and also the largest fishing ground in China. As the first leading cancer in Zhoushan, the age-standardized annual incidence rate of gastric cancer varied from 35 to 40 per 100 000 in 1980-1985, which is higher than the national level (about 25.0 per 100 000). To investigate the risk factors for this common cancer in the coastal areas, we conducted a population-based case-control study in Zhoushan to obtain information on the frequency of consumption and portion size of common foods, and found that intake of certain nutrients in these foods influences the risk of gastric cancer.

MATERIALS AND METHODS

The data-collection period for the study spanned through the whole year of 2001 and comprised all the islands in Zhoushan, Zhejiang Province. The study population included 138 newly diagnosed patients with gastric cancer between December 1, 2000 and November 30, 2001 and 140 controls as a representative sample of residents in the same area.

All the cases were identified at the five largest hospitals in Zhoushan Islands. Of the 138 eligible patients, 10 (7.3%) died before interview, 18 (10.2%) could not be contacted as they were from distant islands, 7 (5.1%) refused to participate. Of the 103 (81 men and 22 women) patients included in the analysis, 56.3% were confirmed by histology according to the Lauren classification[3] and 43.7% by other diagnostic methods including surgery, endoscopy, X-ray and ultrasound. Controls were selected from permanent residents in Zhoushan Islands, frequency matched to the expected distribution of cases by gender, age (10-year groups), and residents of the islands. Of the 140 eligible controls randomly selected from the Zhoushan resident files, 133 (95 men and 38 women) were interviewed, yielding a response rate of 95.0%. Each subject was interviewed face-to-face by trained interviewers.

Dietary information

A questionnaire was designed to collect information on demographic and socio-economic conditions, diet, cigarette smoking, alcohol drinking, history of selected diseases, family history of cancer, occupation, and other factors. Frequency of intake and portion size in a 12-mo period 1 year before the interview were assessed for more than 60 food and beverage items, which included information on dairy products, fruits, meat, processed meat, fish, vegetables and candies, *etc*. These items accounted for over 85% of food intake in Zhoushan residents. For each food, amount consumed was estimated according to models of the more frequently consumed foods. Consumption of seasonal vegetables and fruits was assessed on the basis of average intake during the relevant period of the year.

Nutrient intake

Fifteen priority nutrients and total calories were selected beforehand as previously described[4-6]. Quantitative estimate of cumulative nutrient intake per day in each food was based on food tables derived from the Chinese Food Composition Tables. Total intake of each nutrient was summed over all foods consumed. The Matlab5.0 software was used for processing these procedures by the method of multiplication of matrix[7].

Data analysis and control of confounding

Descriptive analysis of nutrient intake for cases and controls was carried out by computing medians and percentages because of biased distributions of the data, which could not be transformed into normal with logarithmic transformations. The medians were compared by the nonparametric median test.

Then continuous variables of nutrient intake were divided into quartiles based on the distribution in controls, with an approximately equal number of controls in each intake stratum. The amount of intake varied substantially between the sexes, hence sex-specific cutpoints were used for amount of nutrient intake. Risk of gastric cancer associated with dietary factors was estimated by odds ratios (ORs) and its 95% confidence intervals (CIs), using unconditional logistic regression models. Each classified nutrient was introduced into the model as a dummy variable. The lowest level of consumption was used as the reference category in the estimation. All ORs were adjusted for age, economic status (based on monthly family *per capita* income), present residence, educational level and total calories. In addition, ORs for men were further adjusted for cigarette smoking and alcohol drinking, confounding factors common in Chinese men but not in Chinese women (only 5% of women smoke, and 6.7% drink alcohol regularly).

For testing of linear trends, the ordinal nutrient intake variables were treated as continuous variables. In this step, $P \leqslant 0.05$ was considered as evidence for a dose-response relationship. All analyses were carried out by the SPSS version 10.0 software.

RESULTS

Selected characteristics of the study population are shown in Table 1. Due to the frequency-matching procedure by age, gender and present residence, the characteristics of these three variables were similar. Compared to controls, only the age of patients was slightly older (median age 63 years for cases and 60 years for controls). Among

Table 1 Distribution of 103 cases of gastric cancer and 133 controls according to age, gender, address and selected variables

Characteristics	Cases (*n* = 103)	Controls (*n* = 133)	χ^2	*P*
Age (yr)				
Average	3 (30–85)	60 (28–82)		
⩽45	6	20		
46–55	27	32		
56–65	32	38		
66–75	30	38		
76–85	8	5	6.40	0.172
Gender				
Males	81	95		
Females	22	38	1.59	0.210
Present residence[1]				
Large islands	70	76		
Medium islands	17	33		
Small islands	16	24	3.20	0.202
Education (yr)				
<7	43	45		
7–12	58	76		
⩾13	2	12	5.89	0.053
Economic status				
Low	46	30		
Medium	32	44		
High	25	51	12.15	0.002
Cigarette smoking				
Ever-smokers	62	70		
Non-smokers	41	63	1.35	0.246
Alcohol drinking				
Ever-drinkers	58	63		
Non-drinkers	45	70	1.86	0.173

[1]Three categories of islands were classified according to the number of permanent residents on islands: Dinghai, Putuo, and Daishan Islands, which are the three main islands in Zhoushan, predefined as the large islands; the islands on which the number of permanent residents is over 25 000, defined as the medium islands; the residual defined as the small islands.

Table 2 Medians of daily intake of nutrients in gastric cancer cases and controls, Zhoushan, China

Nutrient / d	Males		Females		All	
	Cases (*n* = 81)	Controls (*n* = 95)	Cases (*n* = 22)	Controls (*n* = 38)	Cases (*n* = 103)	Controls (*n* = 133)
Total calories (kJ)	2 963.25	3 073.16	3 002.32[b]	2 420.08[b]	2 984.54	2 937.73
Macronutrients						
Protein (g)	94.21	88.33	98.34[a]	76.92[a]	95.17[a]	85.21[a]
Fat (g)	61.04	65.04	56.23[a]	42.65[a]	60.60	57.48
Saturated fat (g)	8.90	9.44	6.33[a]	4.64[a]	8.70	8.44
Mono-unsaturated fat (g)	22.42	24.47	18.29	14.92	22.38	20.82
Polyunsaturated fat (g)	16.74	16.69	14.43	14.46	16.11	16.23
Fiber (g)	10.11	10.40	9.78	9.39	10.10	10.33
Carbohydrates (g)	403.36	404.93	411.34	287.31	404.19	359.27
Cholesterol (mg)	170.75	136.44	144.57[a]	62.56[a]	160.43[a]	115.02[a]
Micronutrients						
Carotene (μg)	443.54[b]	521.48[b]	455.38	827.38	443.62[a]	555.30[a]
Vitamin A (μg)	135.35[a]	181.01[a]	164.59	175.70	142.13[a]	179.96[a]
Vitamin C (mg)	42.49	38.94	49.29	61.36	43.64	41.04
Vitamin E (mg)	26.12	25.64	21.54	21.46	24.82	24.95
Mineral salts						
Na (mg)	6 700.32	5 074.32	7 000.52[a]	4 960.27[a]	6 734.41[a]	4 963.28[a]
Ca (mg)	464.08	448.26	560.28	460.57	478.91	448.26
Se (μg)	57.35	49.78	53.60	56.02	53.96	52.13

[a]*P*<0.05; [b]*P*<0.10 *vs* others.

non-dietary variables considered, the major determinants of gastric cancer risk were indicators of socio-economic status. For instance, 41.8% of the cases and 33.8% of the controls reported less than 7 years of education, 58.2% of the cases and 66.2% of the controls reported 7 years or more of education. As for the economic status, patients tended to have lower monthly income (44.7% of cases and 22.6% of controls with an average *per capita* income of 36 Chinese Yuan/month or less). No material difference in smoking/drinking habits was observed between cases and controls.

Table 2 shows the medians of daily nutrient intakes in the gastric-cancer cases and the controls according to gender. Overall, the cases reported significantly higher consumption of protein, cholesterol and Na (sodium) than controls, but these differences were significant only in the females. For controls, consumption of carotene and vitamin E was much higher, and on the contrary, the differences were significant in the males.

The multivariate-adjusted ORs for the quartile distributions of the macronutrients (Table 3) showed a significant positive linear trend for the risk of gastric cancer with increasing consumption of protein and cholesterol in males, whereas total fat and carbohydrates in females. The ORs for the highest quartile compared to the lowest quartile of consumption frequency significantly elevated for protein

Table 3 Odds ratios[1] (ORs) and 95% confidence intervals (CIs) of gastric cancer in relation to quartiles of macronutrients by sex, Zhoushan, China

Nutrient / d[2]	Males				*P* for trend	Females				*P* for trend
	Q_1	Q_2	Q_3	Q_4		Q_1	Q_2	Q_3	Q_4	
Total calories	1.0	1.20 (0.50–2.87)	1.02 (0.39–2.64)	1.26 (0.51–3.11)	>0.10	1.0	1.45 (0.27–7.89)	1.41 (0.26–7.74)	2.75 (0.45–16.84)	>0.10
Protein	1.0	3.00 (1.02–8.85)	5.11 (1.26–20.76)	10.30 (1.83–58.12)	0.010	1.0	4.28 (0.50–36.77)	1.71 (0.13–22.37)	6.10 (0.39–94.66)	>0.10
Fat	1.0	1.29 (0.52–3.2)	1.21 (0.46–3.17)	1.01 (0.35–2.92)	>0.10	1.0	1.38 (0.21–8.9)	1.85 (0.23–14.74)	8.26 (1.03–66.51)	0.023
Saturated fat	1.0	2.51 (0.90–6.97)	2.34 (0.81–6.8)	3.24 (1.11–9.49)	0.060	1.0	0.24 (0.02–3.11)	3.34 (0.52–21.44)	3.42 (0.48–24.49)	0.094
Monounsaturated fat	1.0	1.62 (0.67–3.94)	1.24 (0.49–3.17)	1.17 (0.43–3.22)	>0.10	1.0	0.30 (0.03–2.59)	1.83 (0.31–10.76)	1.32 (0.17–10.4)	>0.10
Polyunsaturated fat	1.0	1.21 (0.46–3.17)	1.72 (0.66–4.46)	0.96 (0.33–2.78)	>0.10	1.0	0.21 (0.03–1.37)	0.47 (0.09–2.57)	0.10 (0.01–0.80)	0.068
Fiber	1.0	1.69 (0.58–4.92)	0.69 (0.20–2.37)	2.41 (0.51–11.52)	>0.10	1.0	1.82 (0.30–10.9)	1.9 (0.27–13.44)	0.72 (0.06–8.97)	>0.10
Carbohydrates	1.0	1.39 (0.47–4.11)	1.6 (0.41–6.27)	2.14 (0.35–13.04)	>0.10	1.0	0.94 (0.1–8.57)	3.27 (0.37–28.84)	14.78 (1.11–197.32)	0.024
Cholesterol	1.0	1.08 (0.40–2.87)	2.53 (0.99–6.44)	2.76 (1.01–7.53)	0.050	1.0	6.05 (0.53–69.17)	5.31 (0.44–63.44)	11.9 (0.97–146.53)	0.062

[1]Adjusted for age, present residence, education, economic status, smoking (males only), alcoholics (males only) and total calories intake; [2]Data are ORs, with 95%CIs in parentheses.

Table 4 Odds ratios (ORs)[1] and 95% confidence intervals (CIs) of gastric cancer in relation to quartiles of micronutrients and mineral salts by sex, Zhoushan, China

Nutrient / d[2]	Males				P for trend	Females				P for trend
	Q_1	Q_2	Q_3	Q_4		Q_1	Q_2	Q_3	Q_4	
Carotene	1.0	1.82 (0.81–4.08)	0.40 (0.12–1.35)	0.81 (0.23–2.85)	>0.10	1.0	0.37 (0.08–1.70)	0.37 (0.08–1.78)	-[3]	0.025
Vitamin A	1.0	0.59 (0.24–1.45)	0.91 (0.39–2.15)	0.43 (0.16–1.21)	>0.10	1.0	0.32 (0.05–2.21)	0.55 (0.10–3.14)	0.10 (0.01–0.89)	0.091
Vitamin C	1.0	1.15 (0.42–3.18)	1.40 (0.53–3.67)	0.88 (0.31–2.53)	>0.10	1.0	0.48 (0.09–2.5)	0.73 (0.15–3.6)	0.07 (0.01–0.95)	>0.10
Vitamin E	1.0	0.79 (0.29–2.11)	0.88 (0.34–2.29)	0.77 (0.26–2.26)	>0.10	1.0	0.93 (0.17–5.03)	1.32 (0.24–7.26)	0.95 (0.15–6.16)	>0.10
Na	1.0	1.36 (0.50–3.7)	0.91 (0.33–2.5)	3.22 (1.25–8.26)	0.070	1.0	3.70 (0.43–31.75)	0.75 (0.09–6.62)	8.40 (1.09–64.77)	>0.10
Ca	1.0	1.65 (0.64–4.20)	1.30 (0.46–3.62)	2.37 (0.81–6.91)	>0.10	1.0	2.30 (0.32–16.54)	3.78 (0.44–32.28)	4.79 (0.58–39.17)	>0.10
Se	1.0	0.48 (0.17–1.37)	0.78 (0.26–2.39)	1.23 (0.37–4.09)	>0.10	1.0	1.18 (0.20–6.87)	0.68 (0.11–4.23)	0.75 (0.12–4.68)	>0.10

[1]Adjusted for age, present residence, education, economic status, smoking (males only), alcoholics (males only) and total calories intake; [2]Data are ORs, with 95%CIs in parentheses; -[3]$OR_{Q4\ vs\ Q1}$ and $95\%CI_{Q4\ vs\ Q1}$ could not be calculated because of the null value of cases in the 4[th] group among females.

(OR, 10.30; 95%CI, 1.83-58.12), saturated fat (OR, 3.24; 95%CI, 1.11-9.49) and cholesterol (OR, 2.76; 95%CI, 1.01-7.53) in males. In females the risks remained elevated with increasing consumption of total fat ($OR_{Q4\ vs\ Q1}$, 8.26; 95%CI, 1.03-66.51) and carbohydrates ($OR_{Q4\ vs\ Q1}$, 14.78; 95%CI, 1.11-197.32). A marginally significant inverse linear trend was also observed for frequent consumption of polyunsaturated fat ($OR_{Q4\ vs\ Q1}$, 0.10; 95%CI, 0.01-0.80) with the test for trend (P = 0.068).

The results of the micronutrient-intake (Table 4) uncovered a protective effect of vitamin A, with a marginally significant linear trend that held only for females ($OR_{Q4\ vs\ Q1}$, 0.10; 95%CI, 0.01-0.89). Similarly, a protective effect was seen for the highest category of vitamin C consumption in female cases of gastric cancer (OR, 0.07; 95%CI, 0.01-0.95), but no linear trend was found (P>0.10). In this data set, we found no significant relationship of gastric cancer with intake of vitamin E and carotene, although most OR values suggested a protective effect of them. Results from the analysis of mineral salt intake suggested a significant high-risk effect of sodium, regardless of their gender ($OR_{Q4\ vs\ Q1}$, 3.22; 95%CI, 1.25-8.26 in males; $OR_{Q4\ vs\ Q1}$, 8.4; 95%CI, 1.09-64.77 in females).

Further adjustment for other potential confounding factors, such as green tea drinking, occupation and family history of cancer, did not affect the associations with nutrient intakes. While 44% of the cases were diagnosed by methods other than histological confirmation, exclusion of these cases also did not alter our main findings.

DISCUSSION

The findings of this study confirm that several dietary factors identified elsewhere can also explain the incidence of gastric cancer in Zhoushan, Zhejiang Province, though gastric cancer did not decline in Zhoushan during the last 20 years. We also found that the incidence of gastric cancer in males and females is differently related to the intake of specific nutrients.

The results pertaining to an increased risk of gastric cancer due to the consumption of protein, fat and cholesterol are similar to those reported by Palli *et al*., in Italy[4]. In our study, the relationship between protein, saturated fat and cholesterol intake and gastric cancer was stronger in males after adjustment for other confounding factors. Nitrites and salt in processed and smoked meats, commonly in the Zhoushan diet, are thought to play a role in the etiology of gastric cancer[9]. In this regard, it is possible that saturated fat, cholesterol and protein consumption should be considered as proxy indicators for processed-meat consumption. We also found a protective effect of polyunsaturated fat against gastric cancer particularly in females, which is supported by other studies[10,11].

A positive association with dietary carbohydrates has been reported in several studies of gastric cancer[5,12,13]. In our study, the excess risk associated with carbohydrates contained in rice, noodles, and biscuits in the Chinese diet, could not be explained by education, present residence and economic status, although residual confounding by these or other unmeasured variables remains possible. Furthermore, the risk effect was stronger in females. The mechanism by which high consumption of carbohydrates may increase the risk of gastric cancer is unclear, but several possibilities have been suggested, including physical irritation (especially from rough whole-grain cereals), reduction in gastric mucin, and lowering of gastric pH with promotion of acid-catalyzed nitrosation[14].

The most consistent finding in the relation between diet and gastric cancer is the protective effect of vegetables and fruits[15-17]. A large number of potentially anti-carcinogenic agents are found in these food sources, such as carotenoids, vitamin C, vitamin A, fiber, and vitamin E, *etc*. In our study, we found a strong protective effect of vitamin A and vitamin C consumption against gastric cancer, particularly in females. Although the protective effect of vitamin C against gastric cancer has been mostly ascribed to its ability to inhibit formation of *N*-nitroso compounds from secondary amines and nitrite in the stomach, the role of vitamin C as a free-radical scavenger may be equally important[18,19]. Vitamin A is also a well-known antioxidant, but its protective effect against gastric cancer is only occasionally reported[12,20]. The decrease of gastric cancer risk in association with consumption of dietary fiber has also been observed[21]. However, the mechanism of this protective effect has not yet been identified[6]. Because vegetables and fruits not only are sources of fiber, but are the main contributions of vitamins A and C. Fiber may simply be a good indicator of consumption of plant food. As for the protective effect of vitamin E against gastric cancer, the epidemiologic results are also inconsistent[6,13,22-24]. In view of the anti-oxidant properties of vitamin E, it has the same mechanism as ascorbic acid. Our results are more inclined to support the hypothesis that vitamin E might reduce the risk of gastric cancer.

The analysis of mineral salts suggested that only sodium mainly from salts had an increased risk for gastric cancer, regardless of the gender. Foods that are high in salt or preserved with salt in some form (dried or pickled food) are associated with an increased risk for gastric cancer[1,23,25]. Although the exact mechanism by which salt predisposes to gastric cancer is not known, salt can irritate the gastric cancer mucosa, making it more susceptible to carcinogenic change. Salt may also lead to atrophic gastritis, which is associated with increased risk for gastric cancer[26-29]. Atrophic gastritis can lead to colonization by bacteria that can catalyze the conversion of nitrites to carcinogenic *N*-nitroso compounds[30,31].

Although our findings are consistent with most previous studies of gastric cancer conducted in other countries, several potential limitations of our study should be noted. While the participation rate of the controls was relatively high (95%), only 75% of the eligible cases participated. Since there was generally a 3-mo delay between diagnosis and interview with cases, a few (10%) could not be connected for living in distant islands. Another main reason for non-participation was the death that occurred among cases (7.3%), thus raising the possibility of survival bias. If the identified risk factors could also affect the survival of gastric cancer patients, then exclusion of deceased cases may underestimate the true risks associated with these factors. On the other hand, selection bias, which tends to shift the risk estimates away from unity, should also be minimal since a small percentage of subjects refused to participate. As for the recall bias commonly existed in the dietary survey, efforts have been made to minimize it in various ways, including extensive training of interviewers, use of a standardized questionnaire and models of the more frequently consumed foods. But there were still many other potential recall biases not considered.

An additional limitation is that many nutrients are contained in the same food, and there is some correlation between the intake of certain nutrients, making it difficult to differentiate individual effects. Associations may also appear merely by chance because of the associations analyzed.

In summary, our results from the coastal areas confirm again that the diet plays an important role in the etiology of gastric cancer, and interventions against bad dietary structures may be important for the prevention of gastric cancer.

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