

## RESEARCH COMMUNICATION

## Salt Taste Sensitivity Threshold and Gastric Cancer

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## Abstract

**Background:** Gastric cancer is a major health issue in China. The risk factors are related to the environment and nutrition, including salt intake. Salt taste sensitivity is the capacity to identify the flavor of salt and the salt taste sensitivity threshold (STST) can influence salt appetite. **Methods:** A 1:2 matched hospital based case-control study including 300 cases with newly histological confirmed diagnosis of gastric cancer and 600 controls that were cancer and gastric disease free was performed. A self-designed questionnaire was used to collect information on possible risk factors of gastric cancer, and a salt taste sensitivity test was used to measure the STST for all subjects. Conditional logistic regression was employed to calculate odds ratios (ORs) and 95% confidence intervals (95% CI). **Results:** Salted and preserved meat (adjusted OR=2.12 (1.71-3.67) for  $\leq 3$  times/week; adjusted OR=3.12(2.13-4.76) for  $\geq 4$  times/week), pickled vegetables (3.13 (1.74-5.33) for  $\geq 4$  times/week) and salted fish intake (adjusted OR=1.46 (1.05-1.97) for  $\geq 4$  times/week) demonstrated significant associations with gastric cancer. There is a significant positive association between high STST and gastric cancer, and the adjusted OR was 2.05 (1.68-2.5), and the STST score was positively associated with the frequency of salted and preserved meat. When we used STST $\geq 5$  as a cut point, people with STST $\geq 5$  were at 5.71 (3.18-6.72) times greater risk of gastric cancer than those with STST $\leq 5$ . Also, the cut point of STST  $\geq 5$  had a best sensitivity and specificity for predicting gastric cancer risk detection (sensitivity of 73.7%, specificity of 57.0%). **Conclusion:** Salt and salted food intake are etiological factors for gastric cancer, and a high STST is strongly associated with gastric cancer risk.

**Keywords:** Gastric cancer - risk factors - salt intake - salt taste intensity threshold - China

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## Introduction

Until recently, gastric cancer is the fourth most common cancer world, and is the second most common cause of death from cancer (Stewart and Kleihues, 2003). Its incidence shows wide geographical variation, and almost two-thirds of the cases occur in developing countries and 42% of them in China alone. Although the incidence and mortality rates of gastric cancer, the absolute number of cases is predicted to increase up to the year 2050 (Forman and Burley, 2006). In China, gastric cancer ranked the third among the most common cancer, with an age-standardized incidence of 37.1 and 17.4 cases per 100,000 person-years for men and women, respectively, according to the 2005 national cancer statistics (Yang, 2006). Therefore, prevention of gastric cancer is one of the most important cancer control strategies both in China and around the world.

Salt usually used for improve the taste of food, and it has been hypothesized to be a cause of cancer and an important cause for gastric cancer (WCRF/AICR 2006; WCRF/AICR, 2007). High dietary salt intake may potentiate the colonization of *H pylori* through the increase of surface mucous cell mucin and decrease of gland mucous cell mucin (Fox et al., 1999; Kato et al., 2006). At the molecular level, high dietary salt intake may

potentiate CagA (*H pylori* gene) expression and enhance the ability of CagA to translocate into gastric epithelial cells and enhance the ability of *H pylori* to alter gastric epithelial cell function (Loh et al., 2007).

Many case-control, ecologic, and experimental studies showed that highly salted food may be a risk factor for the development of gastric cancer (WCRF/AICR, 2006). But a recent meta-analysis of case-control and cohort data showed the association between salt and gastric cancer was very weak, only 1.01 and 1.08 per 1g/day, respectively. Also, recent studies is difficulties in estimating the relationship of quantity of salt intake and risk of gastric cancer, and most studies only evaluated the salt preference by subjective feeling. Salt taste sensitivity is the capacity to identify the flavor of salt, salt taste sensitivity threshold can influence salt appetite or salt food preference (Nilsson et al., 1979), and could be associated with the development of gastric cancer. This study aimed to objectively analyze the relationships between salt taste sensitivity threshold (STST) and gastric cancer. We are not aware of any previous study examining such a relationship.

## Materials and Methods

A hospital-based case-control study has been carried out in the Shayin People's Hospital in Shayin County

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of Shanxi Province. The study included 300 patients aged 40-75 years who had histologically confirmed diagnosis of gastric cancer from January 2008 to July 2010. Hospital-based controls were individually matched to case-patients by gender and age ( $\pm 5$  years). Controls were patients selected from Surgical Department, Plastic Surgery Department, ENT Department and Department of Gynecology. Ratio of cases to controls was 1:2. Totally, we had 600 controls that were malignant tumors or digestive tract disorders free.

A self-designed structured questionnaire was used in the study. It included questions on demographic information, family history, lifestyle habits, and dietary habits, diet, lifetime consumptions of all types of alcoholic beverages (beer, wine and distilled spirit).

Face to face interview was performed for all subjects. Two interviewers were trained and were not aware of the study hypothesis. Cancer patients were asked to refer about some lifestyle habits (diet and physical activity) a year before the disease diagnosed. After interviewing for questionnaires, the salt taste sensitivity test was performed to all the subjects. The STST was measured by using NaCl solutions on the tip of the tongue with a dropper. Five drops of the test solution were placed on the tongue. After 10 s closing the mouth, the cases and controls mentioned which taste of usually food was perceived. The solutions were offered in increasing concentrations. Between the tests, the mouth will be washed with distilled water, with 30s intervals among successive tests. The concentrations of each test NaCl solution were classified into ten grades from 0.22 g/L to 58.4 g/L, and the STST value for salt recognizing in normal individuals was 0.015mol/L of NaCl (0.9g/L) (Table 1).

Questions on dietary habits, a main variable of interest, pertained to the following: meal regularity (regular, medium, and irregular), salt food preference (not salty, medium, and salty), and diet preference were classified into three categories: never,  $\leq 3$  times/ week and  $\geq 4$  times/ week. Cigarette smoking was measured in pack-years (number of cigarettes smoked per day/20 $\times$ smoking time (in years)), and divided into three categories: non-smokers; smokers who consumed less than 41 pack/year, and 41 pack/year or more; Alcohol consumption was calculated from the amount of alcohol consumed per day in grams. The subjects were classified into four categories: non-drinkers, drinkers who consumed less than 22.8g alcohol per day, 22.8-45.5g alcohol per day and 45.6 g or more alcohol per day.

The ethics committee of each collaborating institution reviewed and approved the study, and informed consent was obtained from all participants.

*Statistical analysis*

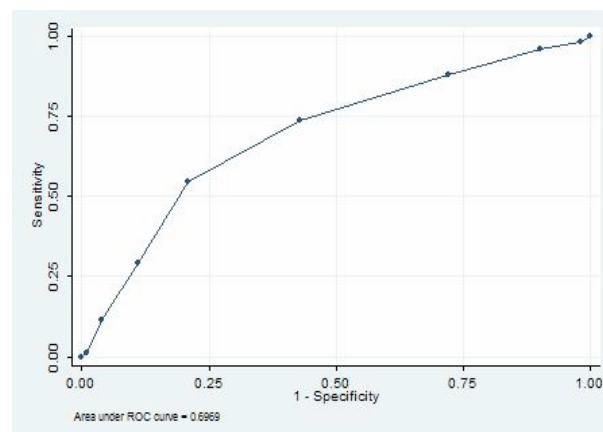
The conditional logistic regression was used to calculate odds ratios (OR), and corresponding 95% confidence intervals (CI) for gastric cancer in relation to exposure of interest. Two models, a) none adjusted b) age, sex, family history, smoking, drinking, fresh fruit and fresh vegetables adjusted, were examined. Tests for trend were computed by fitting conditional logistic regression model to ordinal values representing levels of exposure.

All reported trend test significance levels (p-values) were two-sided ( Woodward, 1999). The chi-square test was used in analyze the difference between groups. The significant level was set at 5%. All the calculations were performed with the STATA 9 software program.

**Results**

All the patients finished questionnaires and STST. The general variables and proportion of selected risk factors among cases and controls was shown in Table 2. Of 300 cases and 600 controls, 71% of them were males and 29% of them were females, the average age of cases and controls were 58.9 and 57.7 years, respectively. The Mean age was 55.4 years for patients and 56.1 years for controls. Cases had lower education level compared with controls. A positive association was found between family history and gastric cancer (2.07 (1.46-2.95)). The alcohol consumption and tobacco consumption also were significantly association with gastric cancer, and we observed a dose-dependent increased risk of gastric cancer with the consumption of alcohol consumption (p for trend <0.001). In contrast, intake of fresh vegetable and fruit were protective against gastric cancer. Those who consumed fresh vegetable and fruit more than 4 times per week was associated with a significantly lower risk compared with never consumption (OR=0.67 (0.36-0.92) for fresh vegetables, p for trend <0.001; OR=0.52 (0.33-0.69) for fresh fruit, p for trend <0.001).

The mean STST score was 4.8 $\pm$ 1.1, and the median NaCl concentration was 3.6 g/L(3.6-7.3) or 0.06(0.06-0.12) Mol/L corresponding to a score of 5(5-6). Then we defined the STST cut point to be 5 score (3.6g/L or 0.06



**Figure 1. ROC Plot of STST for Gastric Cancer Risk**

**Table 1. Concentration of Sodium Chloride**

STST Score	NaCl Concentration		Patients n=300	Controls N=600
	g/L	Mol/L		
1	0.22	0.004	5 (2%)	12 (2%)
2	0.45	0.008	7 (2%)	48 (8%)
3	0.9	0.015	24 (8%)	108(18%)
4	1.8	0.030	43(14%)	174(29%)
5	3.6	0.060	57(19%)	132(22%)
6	7.3	0.120	76(25%)	60(10%)
7	14.6	0.150	54(18%)	42 (7%)
8	29.2	0.500	31(10%)	18 (3%)
9	58.4	1	3 (1%)	6 (1%)

**Table 2. OR and 95% CIs for Lifestyle and Dietary Related Factors and Gastric Cancer**

Characteristics	Patients N=300	Controls N=600	OR (95% CI)	P <sup>1</sup>
Age (yr)				
<50	41 (14%)	101 (17%)	-	>0.05
50-64	189 (63%)	396 (66%)	-	
≥65	70 (23%)	103 (17%)	-	
Mean age (SD)	58.9(0.48)	57.7(0.33)		
Sex				
Male	214 (71%)	428 (71%)		
Female	86 (29%)	172 (29%)		
Education				0.12
Illiterate	96 (42%)	162 (27%)		
Literate	204 (58%)	438 (73%)	0.79(0.59-1.06)	
Smoking (pack-years)				
None-smokers	66 (22%)	162 (27%)	-	<0.001
<41	156 (52%)	276 (46%)	2.27(1.27-4.04)	
≥41	78 (26%)	162 (27%)	2.08(1.07-4.05)	
Drinking (g/day)				
None-drinkers	60 (20%)	197 (33%)	-	<0.001
<22.8	72 (24%)	134 (22%)	2.41(1.51-3.87)	
22.8-45.5	105 (35%)	177 (30%)	3.24(1.97-5.35)	
≥45.6	63 (21%)	92 (15%)	3.96(2.25-6.96)	
Family history of cancer				
No	227 (76%)	521 (87%)	-	<0.001
Yes	73 (24%)	79 (13%)	2.07 (1.46-2.95)	
Fresh vegetable				
never	27 (9%)	42 (7%)	-	<0.001
≤3 times/ week	201 (67%)	318 (53%)	0.97(0.58-1.67)	
≥4 times/week	72 (24%)	240 (40%)	0.67(0.36-0.92)	
Fresh fruit				
never	144 (48%)	180 (30%)	-	<0.001
≤3 times/ week	120 (40%)	282 (47%)	0.72(0.47-0.93)	
≥4 times/week	36 (12%)	138 (23%)	0.52(0.33-0.69)	

**Table 3. OR and 95% CIs for Salt Related Factors and Gastric Cancer**

Salted factors	Cases	Controls	OR <sup>1</sup> (95%CI)	P	OR <sup>2</sup> (95%CI)	P
Salted and preserved meat						
never	45 (15%)	91 (15%)	-			
≤3 times/ week	99 (32%)	241 (40%)	1.54(1.15-2.93)	P=0.01	2.01(1.71-3.67)	<0.001
≥4 times/week	156 (52%)	268 (45%)	1.94(1.44-3.82)	<0.001	2.55(1.37-4.76)	<0.001
Pickled vegetables						
never	120 (40%)	298 (50%)	-		-	-
≤3 times/ week	97 (32%)	219 (37%)	1.11(0.81-1.53)	0.52	1.23(0.59-1.76)	<0.001
≥4 times/week	83 (28%)	83(13.8%)	1.69(1.14-2.17)	<0.001	2.13(1.74-4.33)	<0.001
Salted fish						
never	99 (33%)	201 (35%)				
≤3 times/ week	126 (45%)	282 (47%)	0.87(0.67-1.21)	0.34	0.93(0.57-1.35)	0.56
≥4 times/week	75 (22%)	108 (18%)	1.21(0.92-1.68)	0.07	1.46(0.98-1.97)	0.06
STST score	5.52±1.26	4.4±0.91	1.66(1.48-1.85)	<0.001	2.05 (1.68-2.5)	<0.001
STST≥5	221(73.7%)	258 (43%)	4.03(2.87-5.65)	<0.001	5.71(3.18-6.72)	<0.001

OR<sup>1</sup> for salt related factors and GC were none adjusted. OR<sup>2</sup> were adjusted for age, sex, family history, smoking, drinking, fresh fruit and fresh vegetables.

**Table 4. Accuracy of STST for Predicting Gastric Cancer Risk**

STST Score	Sensitivity	Specificity
1	100.00%	0.00%
2	98.33%	2.00%
3	96.00%	10.00%
4	88.00%	28.00%
5	73.67%	57.00%
6	54.67%	79.00%
7	29.33%	89.00%
8	11.33%	96.00%
9	1.00%	99.00%

Mol/L). The Mean STST score for cases and controls were 5.52±1.26 and 4.4±0.91, respectively (Table 3). There was a significant positive association between increased STST and gastric cancer, and the adjusted OR was 2.05(1.68-2.5). When we use STST≥5 as a cut point, people with STST≥5 were at 5.71 times greater risk of gastric cancer than those who with STST<5 (OR=5.71 (3.18-6.72)). Also, the pickled vegetables and salted meat intake presented significant association with gastric cancer (p<0.05), and a significant dose-response increased risk of gastric cancer was found in salted meat and pickled vegetables (p for trend <0.001). The STST

score was positively associated with the frequency of salted and preserved meat and pickled vegetables, and the  $r$  (correlation coefficient) for them were 0.562 ( $p < 0.05$ ) and 0.433 ( $p < 0.05$ ), respectively.

The accurate of STST for predicting gastric cancer risk was showed in Table 4. The ROC curve (Figure 1) presented A STST  $\geq 5$  had a best sensitivity and specificity for gastric cancer risk detection compared with other threshold (sensitivity for 73.7%, specificity for 57.0%).

## Discussion

The present hospital based case-control study has demonstrated an increased risk of gastric cancer related to the consumption of smoking, drinking, family history of cancer and salted food, also a dose-dependent increased risk of gastric cancer was found for smoking, drinking and salted food. Patients with gastric cancer have a higher mean STST than controls, and that a STST of 3.6g/L (0.03Mol/L) was independently associated with a strong risk of gastric cancer. A STST of 3.6g/L (0.03Mol/L) had a best sensitivity and specificity to predicting gastric cancer risk compared with other salt concentration.

In our study the dietary habits were identified as the risk factors for gastric cancer. Smoking plays a role in developing gastric cancer, which is consistent with the recent IRAC report that tobacco smoke has a causal role in gastric cancer development (Secretan et al., 2009). Also, this study showed drinking is positively association with gastric cancer risk, and this association may be due to the biological effect on carcinogenic of alcoholic beverages to humans (Secretan et al., 2009). The protective effect of fresh vegetable and fruit against gastric cancer was found, and it may be dedicated by antio-oxidants such as ascorbic acid (Cai, 2003). Therefore, intake of more fresh vegetable and fruit may significantly lower the risk of gastric cancer, which is consistent with former epidemiologic studies (Hill, 1998; Ward et al., 1999; Li et al., 2001; Liu et al., 2001). Family aggregation of the gastric cancer has been confirmed in this study with adjusted OR of 2.07 (1.46-2.95). The reason for the first-degree relatives suggested the inherited genetic susceptibility and shared environmental risk factors might contribute to the gastric cancer development.

Our study observed a salted meat intake is relatively common, and a high frequent consumption of salted meat increased the OR for gastric cancer, which is in line with other established positive association between salted meat consumption and risk of gastric cancer (Ward et al., 1997; Cai et al., 2003). Elevated risk of the disease might be attributed to enhance the carcinogenic effects of known gastric carcinogens such as N-methyl-N-nitro-N-nitrosoguanidine (Tatematsu et al., 1975; Takahashi and Hasegawa, 1985), and may also involved the increased cell replication and susceptibility to carcinogenesis from the salt intake.

In our study, we did not found a significantly association between salted fish intake and gastric cancer, however, previous studies indicated Chinese-style salted fish could cause the gastric cancer (Secretan et al., 2009). This may be caused by the economic changes of Chinese

residents, and a reduction in salted fish intake is seen to be less and a more refrigerators use and fresh fish intake are seen, so the number of high frequent consumption of salted fish cases are less, and the power is correspondingly lower to detect the risk of salted fish.

STST is a personal characteristic of the individual and may be eventually be a practical way to evaluate who eats more salt (Spritzer, 1985), and who has the higher preference for salt. STST test has been used for detecting hypertension in studies (Weinberger et al., 1986; Campese, 1994), and it indicated that hypertensive individuals were significantly more salt sensitive than the normotensive individuals (Weinberger, 1996). But for gastric cancer, there is no study used this method to detect its association with gastric cancer, and 24h urinary excretion of salt was usually used for detection the salt intake for this kind of people (Montes et al., 1985; Tsugane et al, 1992), and found strong correlation with gastric cancer mortality which showed weak or non-significantly correlated in dietary salt. Although 24h urinary collection may be an optimal method and objective in estimating routine salt intake, it is impracticable for a large-scale population study, and the results of 24 urinary is not optimal to be used in case-control study because it could not reflect the true salt intake of cases before diagnosis. However, STST test is simpler, cheaper and more acceptable than the STST test, and patients could easily identify the taste before diagnosis.

In our study, we could observe a increased STST is significantly association with gastric cancer, and the adjusted OR was 2.05 (1.68-2.5) compared with the control group with the normal STST, which means the high STST may associate with high intake of salt to induce high risk of gastric cancer, it is in line with the established positive association between salt intake and gastric cancer by 24h urinary collection. Besides, STST  $\geq 5$  had a best sensitivity and specificity for gastric cancer risk detection compared with other threshold (sensitivity for 73.67%, specificity for 57%), which gave an clear threshold for people who are more preference to salt and who should be give more health education or intervention for salt intake.

To date, there is variation method for measuring salt intake consumption levels, and most studies using frequency of salt consumption levels, such as the categorization in our study. Because average salt intake varies across different populations, salt consumption levels considered high in one study might be considered low in another one (Kato et al., 1990). Besides, the salted intake could be from different food, study which calculated the sum of salt consumption is difficult to calculate the salt consumption from all food. Therefore, the method of measuring salt intake consumption from food could induce measurement bias and confounding bias. However, by using of STST test, it could objective reflect the salt preference and ovoid the measurement bias, and it is obviously the salt preference is related to salt consumption, so it is an indirect objective method to measure the salt consumption. In our study we proved the salt intake is significantly related to the increased STST ( $p < 0.05$ ).

Several limitations of this study should be considered.

Firstly, the STST test did not finish before the cancer happened, and the patients may change their salt preference after getting cancer, so the recall bias existed. But we analyzed the relationship between the STST score and salt food intake, and positive association was presented, which indicated the STST could correctly reflect the salt preference. Besides, the recall bias could not be partly neglect in every case-control study, so we used method of reminding patients the questions and the STST were their habits and taste a year before the disease diagnosed. Secondly, the case and controls are selected in a hospital, which may exist selection bias, but we selected controls from Surgical Department, Plastic Surgery Department, ENT Department and Department of Gynecology, the control could better represent the residents in Shanyin County. Finally, the small number of subjects is another limitation, and further studies in a large scale appear warranted.

To summarize, it's the first time to explore the association between the STST and gastric cancer, and the study suggests that STST may be a way to evaluate an inherited characteristics of salt preference, a simple way to verify in clinic the STST to salt. The role of STST has to be further studies to answer the questions raised from the present study.

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