RESEARCH ARTICLE

Salt Processed Food and Gastric Cancer in a Chinese Population

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Abstract

　　To investigate the association between salt processed food and gastric cancer, a hospital based case-control study was conducted in a high risk area of China. One hundred and seven newly diagnosed cases with histological confirmation of gastric cancer and 209 controls were recruited. Information on dietary intake was collected with a validated food frequency questionnaire. Unconditional logistic regression was applied to estimate the odds ratios with adjustment for other potential confounders. Comparing the high intake group with never consumption of salt processed foods, salted meat, pickled vegetables and preserved vegetables were significantly associated with increased risk of gastric cancer. Meanwhile, salt taste preference in diet showed a dose-response relationship with gastric cancer. Our results suggest that consumption of salted meat, pickled and preserved vegetables, are positively associated with gastric cancer. Reduction of salt and salt processed food in diets might be one practical measure to preventing gastric cancer.

Keywords: Gastric cancer - salt processed foods - salt taste preference - risk factor

Introduction

　　Gastric cancer is the second leading cause of cancer deaths, only ranked after lung cancer, although global data have shown a gradual decline in both incidence and mortality (Ferlay et al., 2010). Gastric cancer has remarkable geographic variation across the world, where the most prominent cluster of high rates is seen in eastern Asian countries, such as Japan, Korean and China (de Martel et al., 2013; Lee et al., 2013). China is a high risk country of gastric cancer with the incidence rate of 49.61/105 for males and $22.5/10^5$ for females, which account for nearly half of world cases (47%) (de Martel et al., 2013). There is also a wide geographic variation of this cancer within China. Yanting County, located in the southeast part of the country, is one of the highest risk areas of gastric cancer, with an incidence rate of $138.37/10^5$ for males and $68.04/10^5$ for females, according to 2007 data (Zou et al., 2012; Wang et al., 2013). Although there was a decline of this cancer mortality across the country (Guo et al., 2012), the incidence of cardia gastric carcinoma increased gradually in Yanting area during 1988-2007 (Li et al., 2011).

　　Several environmental and dietary factors have been demonstrated to be associated with gastric cancer. Infection with helicobacter pylori (H. pylori) is a strong and established risk factor for gastric cancer, particularly for non-cardia gastric cancer (Wang et al., 2007; Cavaleiro-Pinto et al., 2011). Smoking, alcohol consumption and dietary factors are among major risk predictors (Ladeiras-

Lopes et al., 2008; Shikata et al., 2008; Duell et al., 2011; Bertuccio et al., 2013; Rohani-Rasaf et al., 2013). Despite that these factors were found to be strongly associated with gastric cancer, great geographic variation in its occurrence indicated that there must be different significant risk factors in different regions.

　　Our preliminary investigations of diets in Yanting area found the local residents generally consumed a high proportion of processed food, such as salted meat, pickled and preserved vegetables, and low intake of fresh fruits. Preserved vegetables in this area were traditionally prepared by keeping tightly packed moist vegetables in a jar for a few weeks or months, allowing fermentation and growth of fungi and yeast. Pickled vegetables were produced by salting Chinese cabbage, carrot/turnip, sweet potato leaves or other vegetables to draw out excess water. These foods may contain carcinogenic N-nitroso compounds, in addition to a high level of salt (Scanlan, 1983). Although some previous studies have reported that salt or salted food was associated with an increased risk of gastric cancer (Larsson et al., 2006; Kim et al., 2010; Peleteiro et al., 2011), others showed weak or non-significant relationships (Sjödahl et al., 2008; Keszei et al., 2012). In addition, not much information has been available on etiological factors for gastric cancer in this high risk area, since no epidemiological studies were conducted there. In this paper, we report results of a case-control study in this area, aiming to examine whether salt processed foods are associated with gastric cancer, taking into account other potential confounding factors.

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Subjects and Methods

Study design and subjects

The study was conducted in Yanting County, Sichuan Province, during 2009 and 2010, with a hospital-based case-control design. Study subjects were recruited from a general hospital in the study area where most local people sought medical service. Selection criteria of cases were male or female patients with a newly histologically confirmed diagnosis of primary GC, (ICD code: C16.0 ~ C16.9) aged between 40 and 75 years and living in the study area for at least 10 years. Hospital-based controls were selected from the same hospital and during the same time period from the departments of surgery, orthopedic, Ear-Nose-Throat (ENT) and gynecology. Patients with cancer at any site and/or a history of digestive diseases or conditions that known to be related with salt and salted food were not recruited as controls. Other inclusion and exclusion criteria for the controls were the same as for the cases. The cases were frequently matched by the controls in terms of age (within 5 years). In the end, 107 cases and 209 controls were recruited in the study. Majority of the cases were adenocarcinoma (94%). Seventy cases (65%) were cardia cancer and most of the remainders were non-cardia cancer (37%). Of the controls, 103 (49%) due to acute injury were selected from surgery department, 43 (39%) from ENT department, 36 (33%) from orthopedic department and 27 (25%) from gynecologic department. This study was approved by the ethic committee of The Chinese University of Hong Kong.

Data collection and dietary assessment

Face to face interviews were conducted by trained investigators in hospital wards. A structured questionnaire was applied to collect information on demographic features, lifestyles, family cancer history, cigarette smoking and alcohol consumption. A food frequency questionnaire (FFQ) was used to obtain subjects' dietary habits and food intake, including the frequency and amount 5 years before diagnosis in the cases and 5 years before interview in the controls. The FFQ was examined to be a reproducible and valid tool in the assessment of food, nutrition and energy intake among local people in a dietary factors related esophageal cancer study (Liu et al., 2014). Salt processed food mainly included salted meat, pickled vegetable, and preserved vegetable, which were homemade and consumed commonly in the study area. For each kind of food, participants were asked to describe how often (per day, per week and per month) and the serving size they had. We made an estimation of average salt processed food intake per week for each subject, expressed as the product of frequency per week and usual serving size (gram). In addition, a question for salt taste preference was also added to the questionnaire, and subjects were asked to rate their salt taste preference in their daily diets (not salty, slightly salty, salty and very salty). A commonly used serving bowl and some food pictures were presented to help subjects recall their past consumption of specific food when investigators collected dietary information. The aims and hypotheses of the study were blind to subjects. The study was introduced to the participants as a diets and health study in order to reduce recall bias.

Data analysis

We first compared the demographic characteristics and relevant dietary factors between the cases and the controls using Chi-square test for categorical variables and t-test for continuous variables. Then, unconditional logistic regression was employed to estimate ORs for the association between salt processed food intake and the risk of GC, in which never consumers were regarded as a reference. Each salted food was categorized into low and high intake in all consumers based on the approximate

Table 1. Basic Characteristics of Study Subjects

	Cases (n= 107)	Controls (n = 209)	*p* value*
Age, mean (SD)	59.1 (8.5)	56.5 (8.4)	0.012
Male, n (%)	88 (82.2)	153 (73.2)	0.074
BMI, mean (SD)	23.0 (1.9)	23.1(2.5)	0.886
Educational level, never school, n (%)	42 (46.7)	104 (51.5)	0.447
Household income, >1200 RMB/year, n (%)	19 (17.8)	123 (58.9)	< 0.001
Family history of cancer, n (%)	43 (40.2)	24 (11.5)	< 0.001
Ever smokers, n (%)	80 (74.8)	125 (59.8)	0.008
Alcohol drinkers, n (%)	80 (74.8)	109 (52.2)	< 0.001
Fresh vegetable intake, >1 time/day, n (%)	83 (77.6)	197 (94.3)	< 0.001
Fresh fruit intake, >1 time/week, n (%)	11 (10.3)	90 (43.1)	< 0.001
Salted meat intake, n (%)			< 0.001
Never	3 (2.8)	24 (11.5)	
Ever	106 (97.2)	185 (88.5)	
Mean intake (SD), g/week	183.9 (93.2)	70.9 (48.9)	< 0.001
Pickled vegetable intake, n (%)			0.001
Never	7 (6.5)	47 (22.5)	
Ever	100 (93.5)	162 (77.5)	
Mean intake (SD), g/week	242.2 (98.6)	175.5 (87.8)	0.005
Preserved vegetable intake, n (%)			< 0.001
Never	36 (33.6)	132 (63.2)	
Ever	71 (66.4)	77 (36.8)	
Mean intake (SD), g/week	103.8(65.5)	53.8 (64.5)	0.021

*Pearson Chi-square test for categorical variables and t-test for continuous variables

Table 2. Logistic Analysis for Gastric Cancer in Relation to Salted Meat Intake

	Cases/controls (n)	Crude OR(95% CI)	Adjusted OR* (95% CI)
Salted meat intake, g/week			
Never	3/24	1	1
≤ 100	37/139	2.13 (0.61, 7.46)	1.74 (0.40, 7.56)
>100	67/46	11.65(3.31, 40.98)	5.95 (1.33, 25.62)
p for trend[†]		< 0.001	< 0.001
Age, yrs			1.03 (0.99, 1.06)
Gender, male			1.64 (0.51, 5.24)
Family history of cancer			2.79 (1.08, 7.10)
Ever smoking			1.37 (0.50, 3.78)
Alcohol drinking			2.92 (1.16, 7.26)
Fresh vegetable intake, >once/day			0.28 (0.11, 0.74)
Fresh fruit intake, >once/week			0.29 (0.13, 0.67)
Household income, >1200 RMB/year			0.24 (0.12, 0.50)

*Adjusted for all other covariates listed on the table; [†]Tests of linear trend in the ORs were performed by fitting models with median values of each salted intake category as a continuous variable

Table 3. Logistic Analysis for Gastric Cancer in Relation to Pickled Vegetable, Preserved Vegetable and Salt Taste Preference

	Cases/ controls (n)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Pickled vegetable intake, g/week			
Never	7/47	1	1
≤ 227	30/81	2.49 (1.01, 6.10)	0.95 (0.31, 2.88)
> 227	70/81	5.80 (2.47, 13.66)	3.09 (1.08, 8.78)
p for trend[†]		< 0.001	0.002
Preserved vegetable intake, g/week			
Never	36/132	1	1
≤ 43	24/57	1.58 (0.87, 2.90)	1.46 (0.63, 3.37)
> 43	47/20	8.68 (4.58, 16.46)	6.33 (2.73,14.69)
p for trend[†]		< 0.001	< 0.001
Salt taste preference			
Not salty	5/46	1	1
Slightly salty	30/138	2.00 (0.73, 5.46)	3.11 (0.96, 10.12)
Salty	36/21	15.77 (5.42, 45.91)	8.13 (2.32, 28.52)
Very salty	36/4	82.80 (20.72, 330.85)	36.19 (7.33, 178.66)
p for trend[‡]		< 0.001	< 0.001

*Adjusted for age, sex, home income, family history of cancer, smoking status, alcohol drinking, fresh vegetables intake and fresh fruit intake; [†]Tests of linear trend in the ORs were performed by fitting models with median values of each category as a continuous variable; [‡]Tests of linear trend in the ORs were performed by fitting models regarding each category as ordinal variable

midpoint of average intake per week. Significantly different covariates between the cases and the controls were included in the models for adjustments, including age, sex, family cancer history (first degree relative with cancer at any site/none), household income per year (> RMB1200/< RMB1200), smoking status (ever smokers/ never smokers), alcohol drinking (ever drinkers/ abstainers), fresh vegetables intake (>once a day/≤once a day) and fresh fruit intake (>once a week/≤once a week). Other variables, such as educational level, BMI, marital status, physical exercises and occupations, were not included because they did not contribute to the models significantly in our analyses. Tests of linear trend in ORs were performed by fitting models with median values of low and high categories as a continuous variable. Data were checked with double-entry using Epi data 3.1. All analyses were performed with SPSS 18.0 for windows and all tests were two-sided and *p*<0.05 were considered statistically significant.

Results

Demographic characteristics and relevant dietary factors between the cases and the controls are shown in Table 1. The cases were older than the controls. Male accounted for 82% and 72% of cases and the controls, respectively. About of in cases and controls did not receive any education. About 75% of the cases were smokers or drinkers, both of which were more common than in the controls. There were 43 cases (40%) who had family cancer history, while only 24 controls (11%) did. The proportions of intake of salted meat, pickled vegetable and preserved vegetable were significantly greater in the cases than in the controls. The average consumption of each food per week was significantly more in the cases than in the controls. In contrast, there was significantly less frequent consumption of fresh vegetables and fruits in the cases than in the controls.

The association between salted meat intake and gastric cancer is shown in Table 2. The crude ORs of gastric cancer increased from 2.1 in the low intake up to 11.7 in the highest group, a positive association remained after other covariates were adjusted. Compared to the never intake group, the high intake was associated with a 74% higher the risk in nearly 6-fold higher (OR=5.95, 95% CI: 1.3, 25.6) in the high intake of 100g or above per week. Other potential confounding factors, including age, male sex and smoking tended to increase the risk, but none of them was significant. However, alcohol drinking and family cancer history was significantly associated with an increased risk. On the other hand, more frequent intake of vegetables or fruits and higher household income were associated with a significantly reduced risk.

Logistic analysis also showed a positive association with both pickled vegetable and preserved vegetable (Table 3), with an exposure-response trend. For pickled vegetable, the crude ORs were 2.5 for the low intake and 5.8 for the high intake category. The odds ratios were attenuated after other covariates were adjusted, but a significantly increased risk remained in the high intake (OR=3.09, 95% CI: 1.08, 8.78). For preserved vegetables, the high intake was related to a 5.3-fold higher

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risk (6.33, 95% CI: 2.73, 14.69), compared to the never intake. Furthermore, a positive association was observed between salt taste preference and gastric cancer, with a clear exposure-response gradient (*p* for trend<0.001). Compared with individuals who preferred non-salty food, those who preferred to slightly salty, salty and very salty food had 2-, 7- and 35-fold increased risk, respectively. Other variables, including age, sex, family cancer history, smoking status, alcohol drinking, fresh vegetables and fruits, were also included in the models listed in Table 3, and they had a similar direction and comparative size of the effects on gastric cancer risk as the model described in Table 2 (data not shown).

Discussion

In this study, we found that consumption of salt processed foods, particularly salted meat, pickled and preserved vegetables, were significantly associated with an increased risk of gastric cancer. In addition, a clear dose-response relationship between salt taste preference and gastric cancer was observed. These results provided some evidence that salt and salted food might contribute to the high risk of gastric cancer in the study area.

A high consumption of salted meat was found to be positively associated with gastric cancer. Preparation for salted meat during the winter season was a folk tradition with long history in China, because no refrigerators were available in rural areas until recently. Pork meat was first preserved with much salt for 1-2 weeks, and then dried in the wind and the sun. Such procedures might lead to formation of N-nitroso compounds from the reaction of nitrosamine and nitrite, which was proven to be carcinogenic to animals and possibly carcinogenic to humans (Scanlan, 1983; Tricker and Preussmann, 2011). In addition to the carcinogens, high salt in the processed meat may increase the risk of gastric cancer, although salt itself is not a carcinogen. The possible explanation for that might be that high salt could directly damage the gastric mucosa, causing susceptibility to gastritis, increasing DNA synthesis and cell proliferation (Charnley and Tannenbaum , 1985). These changes contribute to inducing chronic atrophic gastritis and resulting in the development of gastric carcinoma. Results in our study also showed a trend of dose-response between salt taste preference and risk of this cancer. The subjects who preferred very salty food in diet had a more than 30-fold risk, compared to those preferring to non-salty food, which was in agreement with previous studies reporting that salt was a risk factor for gastric cancer (Nazario et al., 1993; Ramon et al., 1993; Tsugane et al., 2004). Although there was inconsistency regarding results of the association between salted meat and gastric cancer in literatures (Sjödahl et al., 2008; Keszei et al., 2012; Van Den Brandt et al., 2013), recent reviews summarized that increased consumption of processed meat including salted meat was significantly associated with gastric cancer (Larsson et al., 2006; Zhu et al., 2013). Another study conducted in a high risk area of gastric cancer in northwest of China also suggested long-term exposure to salted pork might result in repeated gastric mucosal damage and repair, and

finally in severe dysplasia and malignancy (Yuan et al., 1996). As concluded by the World Cancer Research Fund, salt and salty foods are probable causes of stomach cancer (WCRF, 2007). Our results supported for the positive association between salted meat intake and gastric cancer, and indicated that reducing consumption of salted meat could be one of the preventive measures in such a high risk area.

Salt processed vegetables including pickled and preserved vegetables were found to be commonly consumed in some areas with a high risk of gastric cancer (Yang, 1980). In this study area, nearly 80% of the subjects reported that they ever consumed pickled vegetables. We found that the processed vegetables were positively associated with gastric cancer, even after considering other potential confounders. In addition to high salt in the processed vegetables, it was reported that heavy contamination with fungi might exist as well during reparation and preservation, particularly during preparing preserved vegetable (Cheng et al., 1980). Although some common fungi can reduce nitrate to nitrite, they also increase amines content of pickled vegetables (Li et al., 1986). This can facilitate the endogenous formation of N-nitroso compounds, which have been proven to be strong carcinogenic to several sites of cancer (Scanlan, 1983). Extracts of pickled vegetables from one of the high risk areas in China have shown mutagenic and transforming potency in vitro (Cheng et al., 1980). Furthermore, a synergistic interaction between moldy food and N-nitroso compounds has been reported (Cheng et al., 1980). In fact, most previous studies have reported significant associations between salted vegetable intake and gastric cancer (Lee et al., 1995; Wang et al., 1999; Kim et al., 2010). A meta-analysis showed an increased risk of this cancer with consumption of pickled vegetables in different populations or regions, with OR (95% CI) being 1.89 (1.29-2.77) in Korean, 1.86 (1.61-2.15) in Chinese, and 1.16 (1.04-1.29) in Japanese studies, and 1.14 (0.96-1.35) in studies from other countries (Ren et al., 2012).

Alcohol consumption and family cancer history were also found to be significant risk factors in the study. Most of the alcohol drinkers (93%) consumed liquor in this study area, and consumption of beer and other alcohol containing beverages were not common. The positive association of gastric cancer with alcohol consumption observed in this study agreed with other studies, as summarized in a meta-analysis (Mahjub H and Sadri, 2007). Family cancer history was found to be a risk factor, which was not hard to be understood, because of either similar lifestyles or genetic backgrounds, or both, within family members. Smoking was not found to be significantly assocaited with gastric cancer . More frequent intake of fresh vegetables and fruits were found to have a protective effect on gastric cancer, which was in line with many other studies (Ramon et al., 1993; Lee et al., 1995; Wang et al., 1999; Kim et al., 2010). All of the abovementioned factors, along with demographic characteristics, were adjusted in multivariate analysis estimating the associations between salted processed food and gastric cancer risk in this study.

On the other hand, it is necessary to point out that

information on H. pylori infection status, as one of the important risk factors for gastric cancer, was not available in this study. However, H. pylori infection was reported to be a strong predictor for noncardia cancer, but not for cardia cancer (de Martel et al., 2013). In our study, gastric cardia cancer accounted for 65% of all cases. When we limited the data analysis to the cases with cardia cancer only, the salt processed foods showed similar effects on the occurrence of gastric cancer (data not shown), which suggested that the observed associations with salt processed foods observed might not be fully explained by H. pylori infection. In addition, dietary factors, such as high intake of salt, low intake of vegetables, might act as cofactors with H. pylori infection to increase the risk of gastric cancer (Yamaguchi and Kakizoe, 2001). A Portugal study demonstrated that salt intake was an independent risk factor for gastric cancer, regardless of H. pylori infection status (Peleteiro et al., 2011). More importantly, H. pylori infection also tends to be associated with socioeconomic status, for which we attempted to control in term of household income. Another limitation of the study is recall bias inherent in a case-control study design. However, we made an effort to reduce such bias by using a valid pertinent tool and presenting food pictures in collecting the dietary information. Also, we introduced this study to the cases and the controls as a diet and health survey, rather than a gastric cancer study. The study aim and hypotheses were blind to the subjects and investigators interviewed them in the same style. This nondifferential misclassification might have led to attenuating a true association. Selection bias is another concern in case-control studies. We selected the cases and the controls from the largest hospital that provided medical serves to a major proportion of local residents in the study area, and the response rate in the cases and the controls were high (93.0% and 90.9%, respectively). In addition, the controls were enrolled from various departments of the same hospital as the cases and were not included those who had digestive diseases or any conditions that were known to be associated with these salted foods intake. The cases and the controls were sampled from the same source population, though they might not be representative in the study area. Lastly, the study was also limited by relatively small cancer cases, which reflected in the wide confidence intervals, especially small number in the low intake groups of salted foods. However, we were able to detect statistically significant associations with gastric cancer in the high intake groups, and observed a exposure-response trend in this study.

In conclusion, the results of this study suggest that consumption of salt processed food, including salted meat, pickled and preserved vegetables, were positively associated with gastric cancer. Reduction of salt and salt processed foods intake in diets might be a practical and primary measure for preventing gastric cancer in such a high risk area of China.

Acknowledgements

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