# Processed food consumption and risk of esophageal squamous cell carcinoma: A case-control study in a high risk area

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This study was conducted to investigate the association between consumption of processed foods and esophageal cancer risk. A population-based case-control study was designed. For the present study, 254 patients with esophageal squamous cell carcinoma with pathological diagnoses were selected from Yanting during 2008 and 2010 and 254 community-based controls were selected from the same area, individually matched with cases by age and sex. Data on demographic, lifestyle and dietary factors were collected using food frequency questionnaires. A conditional logistic regression model was used to estimate the odds ratio (OR) with adjustments for potential confounders. Compared to the frequency of <1 time/week, the intake frequency of >3 times/week of preserved vegetables had a significant association with esophageal cancer (OR = 5.01, 95% confidence interval [CI] 2.07, 12.17). In stratified analyses, the OR of increasing intake of preserved vegetables for esophageal cancer were 2.02 in men (95% CI 1.18, 3.48), 3.15 in women (95% CI 1.28, 7.75), 2.41 (95% CI 1.45 4.01) in the persons <65 years old and 1.28 (95% CI 0.35, 4.65) in persons ≥ 65 years old. Consumption of pickled vegetables was not associated significantly with esophageal cancer risk. Intake of salted meat with a frequency of ≥ 1 time/week meant that the OR increased to 2.57 (95%CI 1.02, 6.43), but no significant trend or association in subgroup analysis was observed. Preserved vegetable consumption was associated with increased risk of esophageal cancer, while no association was found with pickled vegetables. (Cancer Sci 2012; 103: 2007–2011)

E sophageal cancer (EC) is the eighth most common cancer and the sixth most common cause of cancer death in the world.[1] China experiences the highest incidence and rates of death from EC worldwide. Among the estimated 482 300 new cases and 406 800 deaths in 2008, more than half occurred in China,[2] where esophageal squamous cell carcinoma (ESCC) was the predominant pathological type.[3] In addition, there is substantial geographic variation of the incidence within the country.[4] Yanting County is one of the high risk areas for ESCC, with an incidence nearly five times that of the national average rate.[4]

Etiological factors of EC have not been clearly documented, and the risk factors may be different between the EU and the USA and Asian countries. In the EU and the USA, tobacco and alcohol drinking are reported to be the main causes/risk factors for EC, contributing to over 90% of case occurrences.[1] In China, the major risk factors are less clear, but dietary factors are believed to play an important role in the occurrence of the disease.[1] Processed food, including preserved vegetables, pickled vegetables and salted meat, which contain N-nitroso compounds, are consumed heavily (in terms of both frequency and amount) in the high risk areas, including Yanting.[5] N-nitroso compounds have the potential to induce the occurrence of EC.[6] This case-control study, conducted in Yanting, investigates the effects of processed food consumption on the risk of ESCC in the Chinese population.

## Materials and methods

The study is a population-based case-control study, which focuses on the investigation of the risk factors of ESCC, especially dietary factors, lifestyle behaviors and socio-demographic factors. The ESCC cases (International Classification of Diseases 10 codes 15.3–15.5) were recruited from the Yanting Tumor Hospital, which serves the whole county. As the only hospital specializing in cancer in the area, the majority of cancer cases were diagnosed and treated in the hospital. The patients eligible for the study were those who: had been diagnosed in the hospital as having primary ESCC from January 2008 to May 2010, with a histological confirmation; had lived in the area for at least 15 years; were aged from 40 to 70 years old; and were alive for the interview. Meanwhile, community controls were selected from individuals living in Yanting. The control individuals were members of the community who had not been diagnosed with cancers while participating in the screening program. The controls were individually matched with cases in terms of age (±5 years) and gender. They had also lived in Yanting for at least 15 years and were aged from 40 to 70 years old. They did not have any cancer at any site and were not related to the patients with ESCC. The screening program was supported by the Ministry of Health, to detect early EC among the individuals who resided in the high-risk areas. There was no charge for the service and it was promoted by the local government. In the end, 254 pairs of patients and controls were recruited and analyzed in the study. The patients included accounted for 78.8% in 2008, 89.7% in 2009 and 85.1% of eligible cases in 2010. Among the non-participants, 32 were experiencing severe illness and 12 had moved to other facilities for treatment. The response rate of the invited controls was more than 95%.

Before data was collected, informed consent was obtained from each subject or the subject's guardian. Two well trained interviewers conducted a face-to-face interview to collect data from both patients and controls during the period from October 2009 to May 2010. The food frequency questionnaire

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(FFQ) first introduced by the National Institute of Cancer was modified based on the local dietary habits.[7] Details regarding frequency and amount of different food items consumed 5 years before the diagnosis (for the cases) or before the interview (for the controls) were collected. The collected data also included lifestyle behaviors, such as tobacco smoking and alcohol drinking, and demographic characteristics, such as age, gender and history of cancer among first-degree relatives.

Information regarding the consumption of preserved vegetables and pickled vegetables was collected separately. Preserved vegetables are made by boiling fresh vegetables and then fermenting them in a concealed container for at least 2 weeks. Pickled vegetables are made by putting fresh vegetables into salted water for approximately 2–3 days. Salted meat is made by processing fresh meat in salt for 1 week and drying it outside for at least 2 weeks. If an answer regarding the intake frequency was fewer than once per month each year, we assigned the subject into the category of no consumption of the food. Subjects who smoked more than 100 cigarettes or with an equivalent use of pipes in their lifetime were defined as ever smokers.[8] If a person stopped smoking for at least 6 months 5 years before the diagnosis (for the cases) or 5 years before the interview (for the controls), he or she was defined as a former smoker.[8] An alcohol drinker was defined as someone having drunk alcohol at least once per month.[9] Someone who was a drinker but stopped more than 5 years before their diagnosis or the interview in the case of controls was defined as a former drinker, and current alcohol drinkers were defined as not having quit drinking alcohol within the 5 years prior to their diagnosis or their interview in the case of controls.[10] Family cancer history was defined as the occurrence of cancer at any site among first-degree relatives, which referred to father, mother and siblings. The research protocol was approved by the Ethics Committee of The Chinese University of Hong Kong.

**Statistical analyses.** All analyses were performed using SAS 9.1 version (SAS Institute, Cary, NC, USA). The categorical variables were analyzed by $\chi^2$-test to measure the differences between the patients and the controls; ordinal variables with more than two levels were analyzed using the Cochran–Armitage trend test. A multivariate conditional logistic regression model was used to estimate the odds ratios and 95% confidence intervals (CI), with adjustment of potential confounding factors. The significance level for all analyses was 0.05 (two-sided test).

Several models were constructed, with processed food items being included in all. Model 1 included age, smoking (never, former or current) and alcohol drinking status (never, former or current) for adjustment; in model 2, age and the consumption frequency of fruits (<1 time/month, <1 time/week or ≥1 time/week) and vegetables (≤1 time/day or >1 time/day) were adjusted. In the final model, all the variables, including preserved vegetables (<1 time/week, ≤3 time/week or >3 time/week), pickled vegetables (<1 time/week, <1 time/day or ≥1 time/day), salted meat (<1 time/month, <1 time/week or ≥1 time/week), age, smoking (never, former or current), alcohol drinking status (never, former or current), the consumption frequency of fruits (<1 time/month, <1 time/week or ≥1 time/week) and vegetables (≤1 time/day or >1 time/day) and annual per capita income were controlled to obtain the final OR. The categorical variables were treated as continuous variables in the trend test analyses. The subgroup analyses were conducted by the classifications of age and sex, and because of the limited sample size, the variables were set as continuous variables in the final logistic model.

## Results

The average age of patients was 59.4 years old, which was 1 year older than the controls (Table 1). No significant

**Table 1. Characteristics of the cases and controls**

|  | Cases | Controls | P-value |
|---|---|---|---|
| Age, years (Mean, SD) | 59.9 (6.2) | 58.8 (5.1) | <0.05 |
| Gender |  |  |  |
| Men | 164 (64.6) | 164 (64.6) |  |
| Women | 90 (35.4) | 90 (35.4) |  |
| Smoking status† (%) |  |  |  |
| Never | 115 (47.3) | 126 (49.8) | >0.05 |
| Former | 22 (9.1) | 11 (4.4) |  |
| Current | 106 (43.6) | 116 (45.9) |  |
| Alcohol drinking† (%) |  |  |  |
| Never | 124 (51.5) | 120 (48.2) | >0.05 |
| Former | 17 (7.1) | 10 (4.0) |  |
| Current | 100 (41.5) | 119 (47.8) |  |
| Family esophageal cancer history (%) |  |  |  |
| No | 171 (67.9) | 218 (87.6) | <0.01 |
| Yes | 81 (32.1) | 31 (12.5) |  |
| Intake frequency of total fruits† (%) |  |  |  |
| <1 time/month | 141 (55.7) | 108 (43.0) | <0.01 |
| <1 time/week | 74 (29.3) | 58 (23.1) |  |
| ≥1 time/week | 38 (15.0) | 85 (33.9) |  |
| Intake frequency of total vegetables (%) |  |  |  |
| ≤1 time/day | 148 (58.5) | 127 (50.2) | >0.05 |
| >1 time/day | 105 (41.5) | 126 (49.8) |  |
| Annual per capita income† (%) |  |  |  |
| <600/year | 98 (40.2) | 78 (32.2) | <0.01 |
| <1200/year | 71 (29.1) | 39 (16.1) |  |
| <3000/year | 50 (20.5) | 62 (25.6) |  |
| ≥3000/year | 25 (10.3) | 63 (26.0) |  |

†Cochran–Armitage Trend test.

difference was observed in the proportions of smoking and alcohol drinking, but 19.6% more of the patients than the controls had a positive EC history among first-degree relatives (P < 0.01) (Table 1).The patients had 18.9% fewer than the controls in the highest frequency category of total fruit intake (P < 0.01), while the total consumption of vegetables was not significantly different between the two groups (P > 0.05) (Table 1). The patients had less annual per capita income than the controls (P < 0.05) (Table 1).

The patients consumed more preserved vegetables than the controls and 26% more patients were in highest frequency intake category (>3 times/week) than the controls (Table 2). The intake of pickled vegetable was comparable between the patients and the controls (Table 2). In contrast, more of the patients consumed salted meat, and 18% more patients were in the highest frequency category (≥1 time/week) (Table 2).

In the multivariate analyses, increased frequencies of preserved vegetables intake were associated with a higher risk of ESCC, in which a clear gradient was observed (Table 2). In the final model, where covariates were adjusted, the OR was 5.01 (95% CI 2.07, 12.17), related to the high intake of preserved vegetables for ESCC and had a significant dose response relationship (Table 2). For pickled vegetables, the OR for ESCC were close to 1.00 in all models, indicating no association, and in the final model, the OR of moderate and high intake frequency (<1 time/day and ≥1 time/day) were 1.18 and 0.66 for ESCC, respectively, without significance (Table 2). In the analysis of the salted meat consumption, OR related to the highest intake frequency (≥1 time/week) were over two times that in the lowest frequency category (<1 time/month) for ESCC in models 1 and 2 (Table 2). With the adjustments of other covariates in the final model, the OR for ESCC increased to 2.57 (95% CI 1.02, 6.43) in the highest intake category (Table 2).

**Table 2. The odds ratios (95% confidence interval) of processed food consumption in models†**

| | Cases n (%) | Controls n (%) | P-value‡ | Crude odds ratio | Model 1 | Model 2 | Final model |
|---|---|---|---|---|---|---|---|
| Intake frequency of preserved vegetable | | | | | | | |
| <1 time/week | 89 (35.2) | 147 (58.1) | <0.01 | 1.00 | 1.00 | 1.00 | 1.00 |
| ≤3 time/week | 72 (28.5) | 80 (31.6) | | 1.68 (1.05, 2.68) | 1.64 (0.93, 2.89) | 1.78 (1.02, 3.09) | 1.10 (0.55, 2.23) |
| >3 time/week | 92 (36.4) | 26 (10.3) | | 5.17 (3.05, 8.74) | 5.58 (2.95, 10.57) | 4.54 (2.49, 8.28) | 5.01 (2.07, 12.17) |
| P for trend | | | | | | | <0.01 |
| Intake frequency of pickled vegetable | | | | | | | |
| <1 time/week | 55 (21.7) | 55 (21.7) | >0.05 | 1.00 | 1.00 | 1.00 | 1.00 |
| <1 time/day | 29 (11.5) | 33 (13.0) | | 0.84 (0.45, 1.59) | 0.86 (0.40, 1.88) | 0.95 (0.44, 2.04) | 1.18 (0.41, 3.43) |
| ≥1 time/day | 169 (66.8) | 164 (65.2) | | 1.03 (0.67, 1.57) | 1.07 (0.62, 1.85) | 1.03 (0.62, 1.71) | 0.66 (0.30, 1.43) |
| P for trend | | | | | | | >0.05 |
| Intake frequency of salted meat | | | | | | | |
| <1 time/month | 46 (18.2) | 66 (26.2) | <0.01 | 1.00 | 1.00 | 1.00 | 1.00 |
| <1 time/week | 81 (32.0) | 105 (41.7) | | 1.11 (0.68, 1.80) | 1.02 (0.55, 1.92) | 1.31 (0.71, 2.43) | 1.79 (0.74, 4.33) |
| ≥1 time/week | 126 (49.8) | 81 (32.1) | | 2.21 (1.36, 3.61) | 2.25 (1.21, 4.18) | 2.85 (1.54, 5.27) | 2.57 (1.02, 6.43) |
| P for trend | | | | | | | >0.05 |

†Age, smoking and alcohol drinking are adjusted in model 1; total consumption of fruits and vegetables are adjusted in model 2; and in the final model, the other two processed foods, age, smoking, alcohol drinking, fruit and vegetable consumption, family esophageal cancer history and annual per capita income are adjusted. ‡Cochran–Armitage trend test.

In the subgroup analyses, higher intake of preserved vegetables was associated with a 3.15-fold OR among women and a 2.02-fold OR among men. Among the individuals <65 years of age, the OR of higher intake of preserved vegetables increased to 2.41 (95% CI 1.45, 4.01), but among the older individuals (≥65 years old), the OR was 1.28 (95% CI 0.35, 4.65) (Table 3). Increasing intake of pickled vegetables and salted meat did not show significant associations with ESCC risk, regardless of sex and age subgroups (Table 3).

## Discussion

In this study, we assessed the role of processed foods in the occurrence of EC in a Chinese population. We took various processed foods into account separately, in particular preserved vegetables and pickled vegetables, which have usually been considered together in previous studies.[11–15] The processed foods had various effects on the ESCC risk.

Preserved and pickled vegetables are processed foods that are made differently and appear to have different effects on ESCC occurrence. Consumption of preserved vegetables was associated with fivefold ESCC risk, but no significant association between pickled vegetables and ESCC risk was found. In Sichuan Province, pickled vegetables are commonly consumed, but preserved vegetable are consumed more in Yanting. Yanting residents consume larger amounts of preserved vegetables over longer periods. In two other high risk areas, Linxian and

Zhuanghe, preserved vegetables are also consumed in larger amounts. In addition to the different preparation procedures, the consumption durations are also different between preserved and pickled vegetables. The consumption duration of one patch of preserved vegetables is a couple of months and at the end of the consumption period, the vegetables in the patch are often contaminated by fungi, but one patch of pickled vegetables is finished within days. Long-term consumption of preserved vegetables is a possible means of carcinogen exposure. In previous studies, investigations of the effects from preserved vegetables and pickled vegetables have not been separated explicitly, which might be a reason for the inconsistent results. Two case-control studies in Yangcheng and Chaoshan observe a significant association between consumption of pickled vegetables and ESCC.[11,14] However, a nested case-control study and a retrospective cohort study in Linxian report a non-significant association of pickled vegetable intake and ESCC risk.[12,13] Yang et al.[15] carry out a case-control study in Yanting area and find a borderline significant effect of frequent intake of pickled vegetable (OR = 2.12, 95% CI 1.00–4.49). The above inconsistent findings might be a consequence of considering various kinds of processed vegetables as pickled vegetables and analyzing them together. Processed vegetables with various processing procedures might have different impacts on ESCC risk. In our study, we separated preserved and pickled vegetables and observed their different associations with EC risk. With the stratification of age and gender, OR increased significantly in both women and men. The effect of preserved vegetables was stronger among younger individuals. The individuals <65 years old faced to the 2.4-fold OR significantly but the OR in older individuals was 1.3-fold high. In this study younger individuals consumed preserved vegetables more frequently than older ones; another possibility was the older patients with high intake might die and could not join in the study. The age variation of effects needed further research for confirmation.

OR of high intake frequency of salted meat was 2.57, although the association did not have significant trend. The non-significant associations were also observed in subgroup analyses with the stratification of age and gender. In studies conducted by De Stefani et al. in Uruguay, a significant contribution of salted meat consumption to high risk of EC is reported, and ESCC risk is found to be increased by more than 60%.[16,17] In the Netherlands Cohort Study, processed meat

**Table 3. Odds ratios (95% confidence interval) of processed foods in subgroup analyses†**

| | Preserved vegetables | Pickled vegetables | Salted meat |
|---|---|---|---|
| Sex | | | |
| Women | 3.15 (1.28, 7.75) | 0.96 (0.46, 2.00) | 1.47 (0.65, 3.32) |
| Men | 2.02 (1.18, 3.48) | 0.81 (0.51, 1.28) | 1.41 (0.84, 2.36) |
| Age classification | | | |
| <65 | 2.41 (1.45, 4.01) | 0.61 (0.36 1.04) | 1.55 (0.89, 2.71) |
| ≥65 | 1.28 (0.35, 4.65) | 2.63 (0.75, 9.21) | 0.97 (0.31, 3.09) |

†The other two processed foods, age, smoking, alcohol drinking, fruit and vegetable consumption, family esophageal cancer history and annual per capita income were adjusted; and preserved vegetables, pickled vegetables and salted meat were treated as continuous variables.

consumption is also found to be associated with increased ESCC risk; the hazard ratio increased 3.47-fold among men.[18] In China, salted meat is not cheap and local residents tend to consume it infrequently and in small amounts. The limited sample size is a possible explanation for the non-significant association in this study, and further analyses are necessary with larger sample sizes and a prospective study design.

Previous studies suggest that processed foods are potential sources of N-nitroso compounds,[19] which induce EC in rat models.[6] The carcinogenecity of N-nitroso compounds is also reported in epidemiological studies. The carcinogenetic effects of N-nitroso compounds are demonstrated in a nested case-control study in Michigan[20] and a cohort study in Germany.[21] In Linxian, another high risk area for EC, high levels of N-nitroso compounds were detected in the food, water sources and the urine of local residents.[5] Compared with individuals from low-risk areas, Linxian individuals had a higher value of background N-nitroso compounds and endogenous formation of N-nitrosamines.[22] In Yanting, the consumption of preserved vegetables possibly exposed people to N-nitroso compounds, playing a critical role in the occurrence of EC in the high risk areas. In contrast, the short preparation and storage period of pickled vegetables might preclude exposure to any great amount of N-nitroso compounds.

Yanting Cancer Research Institute processes all cancer registrations and death reports in the country. All of the ESCC patients with a pathological diagnosis between 2008 and 2010 were recruited for the present study and interviewed at the institute. Furthermore, the controls, with no diagnosed cancer history, especially for upper gastrointestinal cancers, were found by the institute. The participation rate was >80% among patients and >95% among the controls. The patients and the controls were matched individually (1:1), to control the confounding effects of age and gender for the analyses between variables and ESCC risk. In the data analysis, conditional logistic regression was used to investigate the effects of certain factors and to control the influences of confounders. One of the limitations in the present study was the recall bias, which might occur in any case-control study. The patients were possibly more likely than the controls to recall the exposures of risk factors, and to overestimate the risk. However, we tried to minimize the bias: interviewers had standardized training regarding data collection and the subjects were unaware of the hypotheses of the study. Another limitation was that the patients included were not all incident cases, with some being prevalent cases. In the sensitivity analyses, in comparing the incident cases (the interval between diagnosis and interview <3 months) and the prevalent cases in terms of their reported consumption of preserved vegetables, it was found that incident cases reported a significantly higher consumption than the prevalent cases. This implied that actual risk might have been underestimated in the study due to including prevalent cases. Control selection was from the individuals in the screening program, who were from the villages with high incidence of ESCC. Each year, 2000–5000 local residents participate in the screening program and esophagus lesions are found in 7.9% without any clinical symptoms detected. It was another approach of introducing underestimation of the actual risk. This was a case-control study design and data were collected for the FFQ 5 years earlier. It was impossible to estimate the validity of the FFQ, because food patterns had changed with the increase in the socioeconomic level in Yanting. The sample size was limited as well, resulting in a wide 95% CI; however, there was still significant association in the analyses.

In conclusion, preserved vegetable consumption might have a significant association with ESCC risk, especially among men and persons under 65 years old. Pickled vegetables and salted meat did not have significant relationships with ESCC. It will be useful to further study the associations between processed food consumption and ESCC risk separately, with a larger sample size and a prospective study design.

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## Disclosure Statement

The authors have no conflicts of interest to declare.

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