Pre-diagnosis consumption of preserved vegetables and prognosis of invasive oesophageal squamous cell carcinoma: a prospective cohort study in one high-risk area in China

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Abstract

Objective: To investigate the prognostic effect of pre-diagnosis preserved vegetable consumption on oesophageal squamous cell carcinoma (ESCC) in Yanting County, China.

Methods: This prospective cohort study enrolled consecutive patients with ESCC. The pre-diagnosis diet consumption data were collected using a food frequency questionnaire at baseline. Preserved vegetable consumption was categorized into two groups: < 1/week and ≥1/week. Kaplan–Meier survival curve analysis with a log-rank test and a Cox proportional hazard regression model analysis were undertaken to compare the two consumption groups.

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Results: The study enrolled 185 patients (121 males and 64 females) with ESCC. Patients consuming preserved vegetables $\geq$1/week had a median survival time of 41 months, but patients consuming preserved vegetables <1/week did not achieve a median survival time. The adjusted hazard ratio (HR) for an intake of $\geq$1/week was 1.58 (95% confidence interval [CI] 1.01, 2.47). Among 'ever smokers', the HR increased to 2.04 (95% CI 1.10, 3.77) and among 'ever alcohol drinkers', the HR increased to 2.50 (95% CI 1.33, 4.73). Among 'never smokers' or 'never alcohol drinkers', no significant association was observed.
Conclusion: A high consumption of preserved vegetables was associated with a poorer prognosis among patients with ESCC.

Introduction

China has one of the highest burdens of oesophageal cancer (EC), accounting for nearly 50% of new cases and specific deaths worldwide in 2012.[1] From 2003, EC incidence and mortality have been declining in China.[2] In cancer registration areas, the age-standardized incidence rate decreased from 39.5/100 000 to 23.0/100 000 from 1989 to 2008, with an mean annual percentage change of –3.3% (95% confidence interval [CI] –2.8%, –3.7%).[2] Several factors are thought to have contributed to the reduction of EC occurrence, such as construction of a cancer registration system, improved economic status, screening, and dietary interventions. However, EC incidence shows a geographic variation in China; populations from high-risk areas are still suffering from oesophageal squamous cell carcinoma (ESCC), the main pathological type of EC in China.[3] Exploring factors that are significantly associated with the development of ESCC is meaningful for vulnerable people in these high-risk areas.

Preserved vegetables are a traditional food in the Yanting area of China and local residents consume them during several months each year. Consumption of preserved vegetables was reported to be associated with a high risk of ESCC and pre-cancerous lesions from case–control studies.[4,5] In addition, a diet that contained preserved vegetables, pickled vegetables and salted meat, was associated with an odds ratio of 2.84 for ESCC.[6] Preserved vegetable consumption might be one of the aetiological factors for ESCC, however, its contribution to the prognosis of patients remains unclear. This study aimed to investigate the prognostic effect of preserved vegetable consumption among patients with ESCC.

Patients and methods

Study population and design

This prospective cohort study recruited consecutive patients with ESCC between October 2009 and March 2010 at the Department of Cancer Early Detection and Early Treatment, Yanting Cancer Hospital, Mianyang, Sichuan Province, China. All participants lived in Yanting County and were diagnosed with a resectable tumour.

All patients had a pathological diagnosis of ESCC and were incident cases with the interval between diagnosis and interview < 3 months. The exclusion criteria were as follows: (i) survival length < 3 months; (ii) > 70 years old; (iii) migrants to Yanting County; (iv) dementia; (v) memory dysfunction; (vi) American Joint Committee on Cancer stage > II.

Two interviewers (F.S. and L.Z.) collected demographic and other related factors, and baseline dietary data from 1 year before ESCC occurrence. Interviewers used a modified food frequency questionnaire to collect dietary information1 year prior to disease diagnosis.[7] The all cause death registry centre in Yanting was responsible for undertaking follow-up of all patients to 31 December 2016. The overall survival was the primary outcome and was calculated from the date of ESCC diagnosis.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human patients were approved by the Ethical Committee of Beijing Shijitan Hospital, Capital Medical University, Beijing, China (no. 2016061). Written informed consent was obtained from all study participants.

Study variables

Preserved vegetables are a particular type of processed food used in Yanting County and the production process involves boiling and keeping fresh vegetables in a sealed container for fermentation for about 2 weeks. Body mass index (BMI) was estimated by dividing weight in kilograms by current height in squared meters. 'Ever smoker' was defined as smoking more than 100 cigarettes or equivalent use of pipes in their lifetime.[8] 'Ever alcohol drinkers' were individuals that drank alcohol at least once per month.[9] Family cancer history was cancer occurrence among their first-degree genetic relatives (parents, brothers, sisters and offspring).

Data collection

Two health workers from Yanting Cancer Hospital attended a training workshop on data collection using a questionnaire. The questionnaire recorded the preserved vegetable, vegetable and fruit consumption frequency as less than once per month, once to three times per month, once to three times per week, four to six times per week, once per day and twice or more per day.[7] Intake frequency of preserved vegetables was categorized into two groups: <1/week and ≥1/week. The repeatability and validity of the modified questionnaire had been previously tested among the rural population.[7] The study hypothesis was blinded to health workers and participants during the data collection process.

Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows®. The age and BMI of the two preserved vegetable intake groups were analysed using Student's t-test. Smoking, alcohol drinking, total vegetable consumption and family cancer history in the two preserved vegetable intake groups were compared using χ^2-test. Total fruit consumption and mean annual family income in the two preserved vegetable intake groups were compared using Wilcoxon rank-sum test. Median overall survival was estimated using the Kaplan–Meier curve method with log-rank test between the two preserved vegetable intake groups. Hazard ratio (HR) and 95% CI were estimated using a Cox proportional hazard regression model, with further adjustments for age, sex, smoking status and alcohol drinking status. Stratified analysis was conducted by smoking and alcohol drinking stratification. A P-value < 0.05 was considered statistically significant.

Results

This prospective cohort study enrolled 185 patients (121 males and 64 females) with ESCC. A total of 72 patients consumed preserved vegetables <1/week and 113 consumed preserved vegetables ≥1/week (Table 1). The age of patients with a preserved vegetable consumption ≥1/week was significantly higher than patients with an intake <1/week (P = 0.015). Females accounted for 42.5% of patients (48/113) that consumed preserved vegetables ≥1/week compared with 22.2% female patients (16/72) that consumed preserved vegetables <1/week (P < 0.05). Forty-nine of 113 patients (43.4%) with a preserved

Table 1. Demographic and clinical characteristics of patients (n = 185) with oesophageal squamous cell carcinoma categorized according to their frequency of consumption of preserved vegetables in the year prior to diagnosis.

Characteristic	Preserved vegetable consumption rate		Statistical significance[a]
	<1/week n = 72	≥1/week n = 113	
Age, years	60.1 ± 8.07	62.8 ± 7.05	P = 0.015
Sex			P = 0.005
Male	56 (77.8)	65 (57.5)	
Female	16 (22.2)	48 (42.5)	
Body mass index, kg/m^2	22.5 ± 2.62	23.0 ± 3.35	NS
Ever smoker			P = 0.002
No	24 (33.3)	64 (56.6)	
Yes	48 (66.7)	49 (43.4)	
Ever alcohol drinker			P = 0.005
No	28 (38.9)	68 (60.2)	
Yes	44 (61.1)	45 (39.8)	
Total vegetable consumption			NS
≤1/day	38 (52.8)	68 (60.2)	
>1/day	34 (47.2)	45 (39.8)	
Total fruit consumption			NS
<1/month	40 (55.6)	60 (53.1)	
<1/week	21 (29.2)	32 (28.3)	
≥1/week	11 (15.3)	21 (18.6)	
Family cancer history[b,c]			NS
No	44 (62.0)	61 (54.5)	
Yes	27 (38.0)	51 (45.5)	
Mean annual family income, RMB[c]			NS
<600	20 (30.3)	46 (41.8)	
≥600 to <1200	13 (19.7)	27 (24.5)	
≥1200 to <3000	25 (37.9)	21 (19.1)	
≥3000	8 (12.1)	16 (14.5)	

Data presented as mean ± SD or n of patients (%).
[a]Continuous variables were compared using Student's t-test and categorical variables were compared using χ^2-test, except total fruit consumption and mean annual family income, which were compared using Wilcoxon rank-sum test; NS, no significant between-group difference (P ≥ 0.05).
[b]Among first-degree genetic relatives.
[c]Not all study participants were able to recall their family cancer history or were prepared to disclose their mean annual family income.

vegetable intake ≥1/week were smokers compared with 48 of 72 patients (66.7%) who consumed preserved vegetables <1/week being smokers ($P < 0.05$). The proportion of patients who consumed preserved vegetables ≥1/week that also had an alcohol drinking history was significantly lower than patients who consumed preserved vegetables <1/week (45 of 113 [39.8%] versus 44 of 72 [61.1%], respectively; $P < 0.05$). There were no significant differences between the two preserved vegetable consumption groups in terms of BMI, total vegetable consumption, total fruit consumption, family cancer history and mean annual family income.

The median follow-up time was 49 months. Median overall survival time of patients consuming preserved vegetables ≥1/week was 41 months. Patients who consumed preserved vegetables <1/week did not achieve a median overall survival time ($P = 0.035$; Figure 1). The association between survival and preserved vegetable intake was reanalysed by reclassifying the intake frequency into <1/week, <1/day and ≥1/day; and the median overall survival times were not achieved (<1/week), 47 months (<1/day) and 26 months (≥1/day), respectively ($P = 0.032$).

More frequent consumption of preserved vegetables was associated with overall survival; with the adjusted HR for the intake frequency ≥1/week being 1.58 (95% CI 1.01, 2.47) (Table 2). Among patients without a smoking history, preserved vegetable consumption was not associated with overall survival. Among patients with a smoking history, consuming preserved vegetables ≥1/week increased their risk of death by 104% (adjusted HR 2.04; 95% CI 1.10, 3.77). The adjusted HR for consuming preserved vegetables ≥1/week was 0.88 and 2.50 among patients without alcohol drinking and with alcohol drinking ($P < 0.05$ for with alcohol drinking), respectively.

Discussion

This current prospective cohort study demonstrated that more frequent consumption of preserved vegetables was associated with a poorer survival among patients with ESCC who also had a history of smoking or drinking alcohol. The higher rate of preserved vegetable consumption (i.e. ≥1/week) resulted in a 58% increased risk of death among patients with ESCC in Yanting County, China.
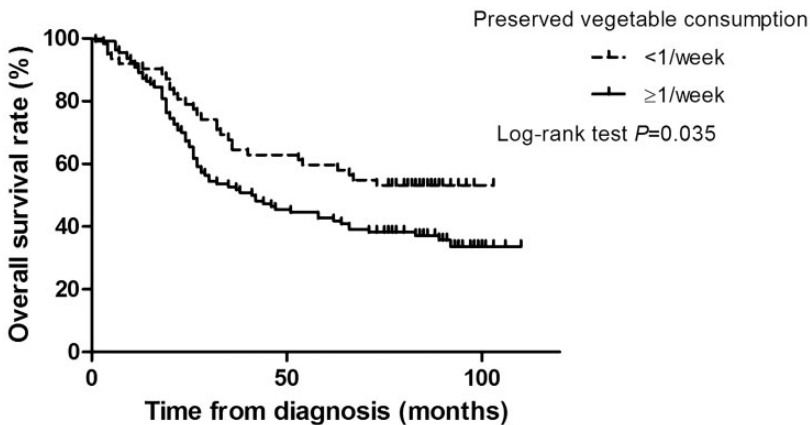

Figure 1. Kaplan–Meier survival curve analysis of patients ($n = 185$) with oesophageal squamous cell carcinoma categorized according to their frequency of consumption of preserved vegetables in the year prior to diagnosis (<1/week versus ≥1/week).

Table 2. Results of Cox proportional hazard regression model analysis of the effect of the rate of preserved vegetable consumption on overall survival.

Subgroup	Preserved vegetable consumption rate	HR crude	95% CI	HR adjusted[a]	95% CI
	<1/week	1	—	1	—
	≥1/week	1.56	1.02, 2.39	1.58	1.01, 2.47
Never smoker	<1/week	1	—	1	—
	≥1/week	0.96	0.52, 1.78	0.98	0.53, 1.81
Ever smoker	<1/week	1	—	1	—
	≥1/week	2.31	1.29, 4.14	2.04	1.10, 3.77
Never drinker	<1/week	1	—	1	—
	≥1/week	0.85	0.48, 1.52	0.88	0.49, 1.59
Ever drinker	<1/week	1	—	1	—
	≥1/week	2.72	1.47, 5.05	2.50	1.33, 4.73

[a]Adjusted for age and sex.
HR, hazard ratio; CI, confidence interval.

Dietary consumption has previously been associated with the prognosis of patients with various malignancies. For example, similar results were observed in non-Hodgkin lymphoma patients: among 'ever smokers', pre-diagnosis exposure to α-carotene foods improved their overall survival (HR 0.4, 95% CI 0.2, 0.9), but among 'never smokers', no beneficial effect was observed (HR 1.5; 95% CI 0.6, 3.6).[10] In this present study, frequent intake of preserved vegetables had a significant relationship with overall survival among 'ever smokers'. In 'ever alcohol drinkers', the association remained significant. Non-Hodgkin lymphoma patients consuming high amounts of vegetables and fruits pre-diagnosis experienced a 42% (HR 0.58; 95% CI 0.38, 0.99) and 27% (HR 0.73; 95% CI 0.54, 0.99) reduction in the risk of death, respectively.[11] High quartile consumption of processed meat was associated with a poorer overall survival for patients with colon cancer (HR 2.13; 95% CI 1.03, 4.43) compared with the lowest quartile processed meat consumption, and it resulted in a 2.29-fold higher recurrence risk for the patients (95% CI 1.19, 4.40).[12] Another cohort study with 2522 postmenopausal breast cancer patients showed that an unhealthy pre-diagnosis diet (high intake of red meat, processed meat and deep-fried fat) produced a 269% higher non-breast cancer death risk (HR 3.69; 95% CI 1.66, 8.17) among the patients.[13] A systematic review pooled the risk ratios of cohort studies to summarize the prognostic effects of diets on cancers and the pooled analysis showed dietary intake significantly affected patients' survival and disease progression.[14] Fish consumption was associated with a 15% reduction in death risk.[14] Alcohol drinking was associated with a poorer survival for hepatocellular carcinoma (relative risk [RR] 1.21), non-Hodgkin lymphoma (RR 1.33), laryngeal and pharyngeal cancer (RR 1.48) and head and neck cancer (RR 1.39).[14] In addition, alcohol consumption increased the breast cancer recurrence risk to 1.21-fold high (95% CI 1.06, 1.39).[14] Pre-diagnosis food intake also affected the prognosis of invasive ovarian cancer patients: high consumption of green leafy vegetables was correlated with a 30% reduced risk of death, high consumption of fish was associated with a 26% reduced risk of death, high intake of fibre was associated with a 31% reduced risk of death, but a high glycaemic

index was associated with an increased risk of death (HR 1.28: 95% CI 1.01, 1.65).[15] However, the dietary effects on ESCC survival has been less well reported. ESCC is the main pathological type of EC in China and the composition of the Chinese diet is different compared with Western diets.[16] Exploring the prognostic effects of local foods on ESCC is important in order to be able to improve patient survival and quality of life. The poorer survival among patients with ESCC who had consumed preserved vegetables in a high-risk area was first reported by this study. This current study reanalysed the association between survival and preserved vegetable intake by reclassifying the intake frequency into < 1/week, < 1/day and ≥1/day; and the correlation was still significant.

Preserved vegetable consumption has been shown to be associated with ESCC risk and precancerous lesions.[4–6] These processed foods are the source of carcinogenic and mutagenic agents, such as N-nitroso compounds.[17] These chemicals possess carcinogenetic effects in animals and promote the development of cancer cells.[18] Even among epidemiological studies, high exposure to N-nitroso compounds resulted in increased mortality in cancer patients.[19,20] People from high-risk areas for ESCC are exposed to high levels of N-nitroso compounds from water and foods.[21] N-nitroso compounds can promote the expression of inducible nitric oxide synthase and cause DNA damage.[22] In rat oesophagus, N-nitroso compounds induced a transitional mutation on the Ha-ras codon 12 G–A; and the activation played a functional role in tumour progression.[23] N-nitroso compounds were capable of inducing over-expression of cyclin E1, cyclin D1, transforming growth factor-alpha and epidermal growth factor receptor in rat oesophagus tissues.[24,25] The consumption of preserved vegetables provides the possibility of being exposed to carcinogenic/mutagenic chemicals, which might result in tumour progression.

The current study had several limitations. First, there were insufficient adjustments made for confounding factors, such as clinical characteristics and related treatments. Secondly, data about tumour recurrence were not available among these patients with resectable tumours.

In conclusion, this current prospective cohort study demonstrated that more frequent consumption of preserved vegetables was associated with a poorer survival among patients with ESCC. These current findings suggest that a public health strategy to reduce the consumption of preserved vegetables should be implemented in areas at high-risk of ESCC.

Declaration of conflicting interests

Funding

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