RESEARCH ARTICLE

Adverse Effects of Preserved Vegetables on Squamous Cell Carcinoma of Esophagus and Precancer Lesions in a High Risk Area

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Abstract

Introduction: Squamous cell carcinoma of esophagus (ESCC) is one of the most common cancers in China. Preserved vegetables are processed foods and consumed in high amounts in the high risk areas for ESCC. This study aimed to investigate the relationships of preserved vegetable consumption with ESCC and precancer lesions. Methods: Cases from Yanting cancer hospital with pathological diagnosis of primary cancer, along with controls and individuals diagnosed with precancer lesions by endoscopy with iodine staining were interviewed. Trained staff collected data on dietary habits 1 year before the interview. An unconditional logistic regression model was used to estimate odds ratios of preserved vegetable consumption for precancer lesions and cancer. Results: Adjusting for potential confounders, intake of preserved vegetables (OR=2.92, 95%CI 1.32~6.47) and longer intake period (OR=5.78, 95%CI 2.26~14.80) were associated with higher risk of ESCC. Compared with lowest intake frequency, the highest was associated with a 3.0-fold risk for precancer lesions and 3.59-fold risk for ESCC (both $p<0.05$). Conclusion: Consumption of preserved vegetables is a risk factor for esophageal lesions in high risk areas. The carcinogenicity of preserved vegetables needs investigation in further studies and the public health strategies for reducing the consumption might be initiated in high risk areas.

Keywords: Preserved vegetable - squamous cell carcinoma of esophagus - precancer lesions - high risk areas

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Introduction

Esophageal cancer (EC) is one of the common cancer in China, account for 16% cancer deaths (He et al., 2011). In 2008, more than half of new cases and deaths of EC worldwide happened in China (Ferlay et al., 2010), and esophageal squamous cell carcinoma (ESCC) was a predominantly pathological type (Lambert and Hainaut, 2007). National average incidence in males of $14.3/10^5$ (He et al., 2011), and had a geographic variation in China (Zhang et al., 2006). Yanting County was one of the high risk areas for ESCC, with the incidence of nearly 5 times higher than the national average rate (Zhang et al., 2006; He et al., 2011; Song et al., 2012).

The etiological factors of ESCC have not been documented clearly, and dietary factors were suspected to play an important role in the occurrence of the disease (Parkin et al., 2005). Preserved vegetable was a processed food and consumed particularly high in Yanting population. Processed food contained high level of N-nitroso compounds (Siddiqi et al., 1991). N-nitroso compounds had the potential carcinogenicity for ESCC occurrence (Fong et al., 1998). In previous studies, intake of preserved vegetables increased relative risk of ESCC to 5-fold high with the comparison to healthy controls (Song et al., 2012). Esophagus hyperplasia and dysplasia were the precancer lesions and associated with ESCC (Wang et al., 2005). But the effects of preserved vegetables on precancer lesion have not been reported. This study aimed to investigate the consumption of preserved vegetables among individuals of normal esophagus, precancer lesions and ESCC and explore the effects on progressing stags of ESCC.

Materials and Methods

This was a frequency-matched study. Individuals of control and precancer lesions were matched with cases of ESCC by age and sex. Age ranged from 40 to 69 and matched by 5-year interval.

ESCC cases were recruited from Yanting Cancer Hospital. The included cases were Yanting local people, aged from 40 to 69, and diagnosed of primary ESCC with pathological evidence between April 2012 and October

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2012. The case individuals were incident patients, that the interval between diagnosis date and interview was less than 3 months. The control and precancer lesion individuals came from the population free of cancer history, participating the screening program of EC between April 2012 and October 2012. EC screening program were implemented among Yanting local people aging 40 to 69 years, and endoscope with iodine staining was introduced to detect the precancer lesions (Dong et al., 2011). "Control" was the individuals defined as normal status; and "precancer lesions" were the individuals with abnormal status detected by endoscopy with iodine staining (Dong et al., 2011).

Preserved vegetables were the processed food particular in Yanting. The processing procedure was that fresh vegetables were first boiled and then keep in a sealed container for fermentation about 2 weeks. Body mass index (BMI) was estimated by dividing weight in kilograms by current height in meters squared. Ever smoker was defined as smoking more than 100 cigarettes or equivalent use of pipes in their lifetime (Pandeya et al., 2008). Ever alcohol drinker were the individuals had drunk alcohol at least once per month (Pandeya et al., 2009). Family EC history was EC occurrence among the first-degree genetic relatives (parents, siblings and offspring).

Two health workers from Yanting Cancer Hospital attended the workshop training on data collection. With written consent, interviewers collected the socio-economic, dietary and other lifestyle data 1-year prior to the interview for control, procancer lesions and ESCC individuals through Modified Food frequency questionnaire.

Statistical Analysis

SAS 9.0 was used to analyze the data. Difference of age and BMI between 3 groups was estimated in ANOVA tests, and education level, smoking status, alcohol drinking status, family cancer history of EC, fruit intake frequency and characteristics of preserved vegetable consumption were conducted in Mantel Haenszel test in the 3 groups. Odds ratio (OR) and 95% confidence interval of preserved vegetables in precancer lesions and ESCC cases with reference to control were estimated by unconditional logistic regression, with further adjustments of age, smoking, alcohol drinking, family history of EC, fruit intake, education level and BMI. The trend of OR was obtained by setting the categorical variables to the continuous ones in logistic model. All the tests were 2 sided with the significant level of 0.05.

Results

Between individuals with normal esophagus, precancer lesions and ESCC, age, sex, BMI, education level smoking and alcohol drinking status did not distributed differently (Table 1). Based on status of esophagus, the proportion of family EC history had a positive trend and higher intake frequency of fruits had an inverse trend from normal esophagus to ESCC (Table 1).

With adjustments of potential confounders, ORs of preserved vegetable consumption and intake length

Table 1. Characteristics Between Individuals of Control, Precancer Lesions and ESCC

	Control n (%)	Precancer lesions, n (%)	ESCC n (%)	*p*
Age (mean±SD)	58.7±6.3	58.6±6.1	58.9±6.0	0.94*
Sex				
Male	51 (70.8)	51 (70.8)	51 (70.8)	
Female	21 (29.2)	21 (29.2)	21 (29.2)	
BMI (mean±SD, kg/m^2)	22.9±3.4	22.4±3.0	22.9±3.2	0.59*
Education level				0.77
≤primary school	50 (69.4)	48 (70.6)	51 (71.8)	
>primary school	22 (30.6)	20 (29.4)	20 (28.2)	
Smoking				0.2
Never	32 (44.4)	36 (50.0)	27 (37.5)	
Ever	40 (55.6)	36 (50.0)	45 (62.5)	
Alcohol drinking				0.39
Never	33 (45.8)	39 (54.2)	31 (43.1)	
Ever	39 (54.2)	33 (45.8)	41 (56.9)	
Family history of esophageal cancer				<0.001
No	63 (88.7)	59 (85.5)	45 (62.5)	
Yes	8 (11.3)	10 (14.5)	27 (37.5)	
Fruit intake frequency				<0.001
<1/month	27 (38.0)	31 (43.7)	47 (65.3)	
<1/week	20 (28.2)	17 (23.9)	19 (26.4)	
≥1/week	24 (33.8)	23 (32.4)	6 (8.3)	

*ANOVA test between groups

Table 2. Associations of Preserved Vegetables with Precancer Lesions and ESCC*

	Control, n (%)	Precancer lesions, n (%)	OR_{crude} (95%CI)	OR_{adj} (95%CI)	ESCC, n (%)	OR_{crude} (95%CI)	OR_{adj} (95%CI)	*p*
Intake of preserved vegetables								0.03
No	36 (50.0)	22 (30.6)	1.00	1.00	19 (26.4)	1.00	1.00	
Yes	36 (50.0)	50 (69.4)	2.27 (1.15, 4.49)	2.06 (0.99, 4.29)	53 (73.6)	2.79 (1.39, 5.61)	2.92 (1.32, 6.47)	
Intake length per year (month)								<0.001
0	36 (50.7)	22 (31.0)	1.00	1.00	19 (27.9)	1.00	1.00	
<3	18 (25.4)	25 (35.2)	2.27 (1.02, 5.08)	2.04 (0.86, 4.85)	6 (8.8)	0.63 (0.22, 1.86)	0.54 (0.16, 1.82)	
≥3	17 (23.9)	24 (33.8)	2.31 (1.02, 5.23)	2.19 (0.89, 5.40)	43 (63.2)	4.79 (2.18, 10.56)	5.78 (2.26, 14.80)	
p_{trend}			0.12			<0.001		
Intake frequency								<0.01
<1/month	38 (52.8)	23 (32.4)	1.00	1.00	19 (28.8)	1.00	1.00	
<1/week	13 (18.1)	9 (12.7)	1.14 (0.42, 3.09)	1.06 (0.33, 3.35)	4 (6.1)	0.62 (0.18, 2.15)	0.86 (0.21, 3.50)	
≥1/week	21 (29.2)	39 (54.9)	3.07 (1.46, 6.44)	3.00 (1.36, 6.61)	43 (65.2)	4.10 (1.92, 8.75)	3.59 (1.55, 8.31)	
p_{trend}			<0.01			<0.001		

*adjusting age, BMI, education level, smoking, alcohol drinking, family history of EC and fruit intake

Table 3. Effects of Preserved Vegetables on Esophageal Diseases with Stratification of Fruit Intake*

Fruit intake frequency	Preserved vegetable intake frequency	Precancer lesions OR	Precancer lesions 95%CI	ESCC OR	ESCC 95%CI
<1/month	<1/month				
	<1/week	0.97	0.17, 5.64	0.66	0.11, 4.16
	≥1/week	3.97	1.32, 11.93	5.65	2.02, 15.82
≥1/month	<1/month				
	<1/week	0.95	0.26, 3.50	0.61	0.11, 3.41
	≥1/week	2.59	1.05, 6.39	2.16	0.72, 6.46

*adjusting age, BMI, education level, smoking, alcohol drinking, family history of EC and fruit intake

increased for precancer lesions, but the association was not significant; OR of highest frequency of preserved vegetables was 3.00 (95%CI 1.36, 6.61) and had a significant trend with precancer lesions (Table 2). Compared with control individuals, for ESCC cases OR of preserved vegetable consumption was 2.92, the intake length of at least 3 months per year increased the OR to 5.78 and intake frequency of ≥1/week elevated the OR to 3.59-fold, all of the comparisons in significant level ; ORs of intake length and frequency, both had significant trend with ESCC (Table 2).

Among individuals seldom consuming fruit, frequent consumption of preserved vegetables was associated with precancer lesions and ESCC significantly ($p<0.05$); among individuals consuming fruit at least once per month, though OR of highest frequency increased to more than 2-fold high, the association did not get significance with ESCC (Table 3).

Discussion

This study included three groups of individuals and the intake characteristics of preserved vegetables were described between the groups. With the comparison to control individuals, the intake length and frequency was significantly higher in individuals of precancer lesion and ESCC, and the adjusted ORs were 3.00 and 3.59, respectively ($p<0.05$). ORs of intake length and frequency even had a significant trend with ESCC.

In Yanting, one of the high-incidence sites of EC, people without symptoms of EC participated into the screening project and received the detection by endoscopy with iodine staining on esophagus (Dong et al., 2011). The positive cases by endoscopy were then assigned biopsy for histological tests in the diagnosis of normal, acanthosis, esophagitis, basal cell hyperplasia, mild squamous dysplasia, moderate squamous dysplasia, severe squamous dysplasia, not otherwise specified squamous dysplasia, squamous carcinoma in situ and squamous cell carcinoma (Wang et al., 2005; Dong et al., 2011). Squamous dysplasia and carcinoma in situ, but not acanthosis, esophagitis and hyperplasia, were the precursors associated with high risk of ESCC significantly (Wang et al., 2005). Some of the precancer individuals had squamous dysplasia and carcinoma in situ, and preserved vegetable consumption in precancer lesion subjects was higher than controls but lower than ESCC cases, indicating the carcinogenicity of preserved vegetables to EC.

Preserved vegetable was one kind of processed foods and the contribution from processed food consumption on increased EC risk was reported from many previous studies. De Stefani E reported that consuming salted meat, another kind of processed foods, was associated with higher risk of squamous cell carcinoma of esophagus, no matter in one-site or multi-site case control studies (De Stefani et al., 1999; De Stefani et al., 2003; De Stefani et al., 2009). In Netherland, one cohort study also presented the similar association between processed meat and ESCC, with the HR being 3.47 (Keszei et al., 2012). Further importantly, many studies in the high risk areas of EC in China reported the significant association between pickled vegetables and EC (Wang et al., 1992; Li and Yu, 2003; Sun et al., 2010). A meta-analysis summarized that consuming pickled vegetables was a significant risk factor for ESCC, the estimated risk being 2.32 (95%CI 1.92, 2.81) (Islami et al., 2009). Previously, we conducted a population-based case-control study in Yanting and OR of highest intake frequency of preserved vegetable was 5.01 for ESCC (Song et al., 2012). These retrospective studies showed the significant risk from processed vegetable consumption on ESCC, but non-significant associations were showed in Linxian by a nested case-control (Guo et al., 1994) and retrospective cohort designs (Yu et al., 1993). The discrepant results needed further analyses in prospective design.

Mechanisms: Processed foods contained high level of N-nitroso compounds (Siddiqi et al., 1991; Ribeiro et al., 1996) and the consumption was particularly high in high risk areas (Kamangar et al., 2009). The carcinogenicity of N-nitroso compounds on EC was reported in both animal studies (Fong et al., 1998) and population studies (Sullivan et al., 1998; Straif et al., 2000). In the high risk areas of EC, such as Linxian, Shantou and Nan'ao, peoples exposed to higher level of N-nitroso compounds than low risk areas (Lu et al., 1986; Ribeiro et al., 1996; Lin et al., 2002; Lin et al., 2003; Lin et al., 2009). N-nitroso compounds were the potential carcinogens from preserved vegetable consumption to increase the high risk of ESCC.

Protective effects from fruit: Fruit consumption had a protective effect against the occurrence of ESCC, reported from the cohort and multi-center retrospective studies in United States (Freedman et al., 2007; Navarro Silvera et al., 2008) and Japan (Yamaji et al., 2008). And in China both the Shanghai cohort (Fan et al., 2008) and Linxian General Population Trial cohort studies (Tran et al., 2005) presented the beneficial effects of consuming fruit against ESCC. Fruit contained high levels of vitamins, minerals, fiber and other antioxidants, and eating fruits increased the concentration of the elements in plasma (Broekmans et al., 2000). Additionally, fruit juice could inhibit the genotoxicity and endogenous formation of N-nitroso compounds (Ohsawa et al., 2003), and increase the plasma capacity of antioxidation (Pedersen et al., 2000). Ascorbic acid (vitamin C) was reported to protect the nitrosame-induced cytotoxcity, genotoxicity and DNA damage in human hepatoma cell line (Arranz et al., 2007; Erkekoglu and Baydar, 2010). In-vivo, vitamin C could also reduce apoptosis in human leukemia and hepatoma cell lines, induced from N-nitrosopiperidine

and N-nitrosodibutylamine (Garcia et al., 2009). Therefore the ascorbic acid from fruit might act as the protectors and reduced the potential carcinogenicity of N-nitroso compounds, and among the individuals consuming fruits, we observed a non-significant risk association with ESCC.

Potential limitations also existed in our study. The data was collected retrospectively and information bias might occur during the collection. Limited sample size was another drawback of the study, further study with larger sample size being in process. The precancer lesions were not homogeneous, including acanthosis, esophagitis, dysplasia and carcinoma in situ, which was impossible to estimate the association strength of preserved vegetables for particular lesion.

In conclusion, preserved vegetables in Yanting possibly contained carcinogens and the intake was associated with increasing risk for precancer lesions and ESCC. The carcinogenicity of preserved vegetables was warranted to be investigated in further studies. The implementation of reduction in preserved vegetable consumption in the high risk areas might need to be carried out.

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