

Increased risk of esophageal squamous cell carcinoma associated with frequent and long-term consumption of salted meat and salted fat

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Abstract

Objective: This study aimed to investigate the association between the consumption of salted meat and salted fat and esophageal cancer risk among individuals with normal esophageal mucosa or esophagitis.

Methods: This case-control study enrolled 216 individuals from Yanting County. Information on the consumption of salted meat and salted fat was collected using a food-frequency questionnaire validated among Yanting people.

Results: Higher intake frequencies (\geq once a week) of salted meat and salted fat were associated with 2.40-fold and 7.37-fold increased risks of esophageal cancer among individuals with normal esophageal mucosa, while long-term intakes (\geq 6 months) increased the risks by 6.87-fold and 85.45-fold, respectively. Similarly, the odds ratios (ORs) of patients with esophagitis developing esophageal cancer from frequent intakes of salted meat and salted fat were 6.48 and 5.05, respectively, and the ORs associated with long-term intakes were 44.38 and 74.90, respectively.

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Conclusions: Frequent and long-term consumption of salted meat and salted fat could increase the risk of esophageal cancer in individuals from Yanting with normal esophageal mucosa or esophagitis. Efforts should thus be made to reduce the consumption of these foods among people in this region.

Keywords

Esophageal cancer, esophagitis, esophagus mucosa, salted meat, salted fat, diet

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Introduction

Esophageal cancer (EC) is a major challenge in China, with nearly 50% of all EC cases and deaths worldwide in 2012 occurring in China.¹ EC became the eighth most common cancer in 2018 with almost 600,000 new cases annually, of which about 80% occurred in developing countries.² However, the incidence of EC in China varies geographically, with a high incidence in Yanting County. The reported national age-standardized incidence and mortality of EC were $14/10^5$ and $10/10^5$, respectively; however, these figures were 5 to 8-fold higher in Yanting County.³ To address this challenge, Yanting government initiated a county-level screening program to detect precancerous EC lesions in 2006,⁴ and conducted some studies to explore the significant risk factors among individuals in Yanting. Dietary factors and behavior have been considered to affect the risk of EC in Yanting.⁵⁻⁷ Fruits contain some bioactive compounds with anticancer effects,^{8,9} and inadequate consumption of fruit and peanuts was reported to increase the cancer risk.^{10,11} In contrast, the frequent consumption of preserved vegetables significantly increased the risk of EC and precancerous lesions.^{12,13} Salted meat and salted fat are other processed foods with a long history of consumption in

Yanting, and the long-term storage of these foods leads to the possible generation of N-nitroso compounds and precursors.^{14,15} The Netherlands Cohort study showed that a $0.1 \mu\text{g}/\text{day}$ increase in the intake of N-nitroso compounds was associated with a 15% to 19% increase in the risk of EC.¹⁶ Given the carcinogenic potential of salted meat consumption, we conducted a case-control study to investigate the association between intakes of salted meat and salted fat and EC risk in individuals in Yanting, including people with normal esophageal mucosa and patients with esophagitis.

Methods

Ethical approval and informed consent

This study was performed in accordance with the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University (2018 Fast-track 5). The need for informed consent was waived because the study involved a retrospective analysis of an available database with no accessible identifiable information.

Patients

We designed a frequency-matched, case-control study including 72 individuals with

normal esophageal mucosa, 72 with esophagitis, and 72 with esophageal squamous cell carcinoma (ESCC). The groups were matched in terms of sex and 5-year age intervals.

Consecutive patients aged 40 to 69 years with a pathological diagnosis of primary ESCC were recruited from Yanting Cancer Hospital. The interval between diagnosis and interview was <3 months in all cases. Control individuals aged 40 to 69 years were confirmed to have normal esophageal mucosa by endoscopy plus iodine staining. Individuals aged 40 to 69 years diagnosed with esophagitis based on clinical endoscopy and abnormal iodine staining of the esophagus mucosa were also recruited. All individuals were recruited between April 2012 and October 2012.

Exposure

Salted meat and salted fat are produced by submerging fresh meat and fat in salt for 1 week, followed by dehydration by air-drying. The recorded intake frequencies were <once a month, <once a week, and \geq once a week, and the durations of intake were <3 months, <6 months, and \geq 6 months per year. Consuming preserved vegetables, fruit, corn, and tea <once a month was defined as 'no consumption'. Body mass index (BMI) was estimated based on height (m^2) divided by weight (kg). Individuals who smoked >100 cigarettes or equivalent use of a pipe during their lifetime were defined as 'ever smokers'.¹⁷ Individuals who drank alcohol at least once a month were defined as 'ever drinkers'.¹⁸ A positive family history of EC was defined as EC occurrence among first-degree genetic relatives (parents, siblings, and offspring).

Two health workers from Yanting Cancer Hospital attended workshop training on data collection and collected the socioeconomic, dietary, and other lifestyle

data 1 year prior to the interviews, using a modified food-frequency questionnaire. The validity and reproducibility of the questionnaire has previously been evaluated among the Yanting population.¹⁹

Statistical analysis

Data were analyzed using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). Univariate analysis using Spearman's correlation test was conducted to compare factors among the normal control, esophagitis, and ESCC groups. Trends in intake frequencies and duration of consumption of salted meat and salted fat in ESCC and esophagitis cases were tested by Spearman's correlation test with reference to the normal controls. Odds ratios (ORs) and 95% confidence intervals (CI) of intake frequencies and durations of consumption of salted meat and salted fat were estimated by unconditional logistic regression, with further adjustments for age, sex, family history of EC, and intakes of fruit, corn, and preserved vegetables. All tests were two-sided with a significance level of 0.05.

Results

There were no significant differences in age and sex among the three groups (Table 1). BMI, education level, and average annual family income were also distributed similarly in all three groups. Individuals with normal esophageal mucosa and esophagitis also had similar smoking, alcohol-drinking, and tea-drinking histories to individuals with ESCC (Table 2). However, significantly more patients with ESCC had a positive family history of EC compared with individuals with normal esophageal mucosa or esophagitis ($P < 0.001$). Spearman's correlation analysis showed significant correlations among the normal control, esophagitis, and ESCC groups in terms of

Table 1. Association between general characteristics and esophageal diseases.

	Normal (n = 72)	Esophagitis (n = 72)	ESCC (n = 72)	P value*
Age, mean ± SD	58.7 ± 6.33	58.6 ± 6.14	58.9 ± 6.00	0.896
Sex, n(%)				>0.95
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 ± 3.37	22.4 ± 3.00	22.9 ± 3.21	0.570
Education level, n (%)				0.823
≥High school	22 (30.6)	20 (29.4)	20 (28.2)	
Primary school	24 (33.3)	22 (32.4)	29 (40.8)	
<Primary school	26 (36.1)	26 (38.2)	22 (31.0)	
Average annual family income (RMB), n (%)				0.517
≤600	23 (35.4)	21 (30.0)	15 (21.1)	
≤1200	12 (18.5)	12 (17.1)	23 (32.4)	
≤3000	16 (24.6)	14 (20.0)	19 (26.8)	
>3000	14 (21.5)	23 (32.9)	14 (19.7)	

*Spearman's correlation test. ESCC, esophageal squamous cell carcinoma; SD, standard deviation; BMI, body mass index

Table 2. Distribution of risk factors between cases with esophageal diseases.

	Normal (n = 72)	Esophagitis (n = 72)	ESCC (n = 72)	P value*
Smoking, n(%)				0.404
Never	32 (44.4)	36 (50.0)	27 (37.5)	
Ever	40 (55.6)	36 (50.0)	45 (62.5)	
Alcohol drinking, n (%)				0.740
Never	33 (45.8)	39 (54.2)	31 (43.1)	
Ever	39 (54.2)	33 (45.8)	41 (56.9)	
Family cancer history, n (%)				0.001
No	50 (69.4)	51 (70.8)	30 (41.7)	
Yes	22 (30.6)	21 (29.2)	42 (58.3)	
Family EC history in first-degree relatives, n (%)				<0.001
No	63 (88.7)	59 (85.5)	17 (38.6)	
Yes	8 (11.3)	10 (14.5)	27 (61.4)	
Fruit consumption, n (%)				<0.001
No	27 (38.0)	31 (43.7)	47 (65.3)	
Yes	54 (62.0)	40 (56.3)	25 (34.7)	
Preserved vegetable consumption, n (%)				0.003
No	36 (50.0)	22 (30.6)	19 (26.4)	
Yes	36 (50.0)	50 (69.4)	53 (73.6)	
Corn consumption, n (%)				<0.001
No	40 (55.6)	27 (38.0)	17 (23.6)	
Yes	32 (44.4)	44 (62.0)	55 (76.4)	
Tea drinking, n (%)				0.304
No	24 (33.3)	27 (37.5)	30 (41.7)	
Yes	48 (66.7)	45 (62.5)	42 (58.2)	

*Spearman's correlation test. ESCC, esophageal squamous cell carcinoma; EC, esophageal cancer.

consumption of fresh fruit ($P < 0.001$), preserved vegetables ($P = 0.003$), and corn ($P < 0.001$) (Table 2).

Significantly fewer individuals with normal esophageal mucosa or esophagitis consumed salted meat at least once a week and significantly fewer consumed salted meat for at least 6 months per year compared with patients with ESCC (both $P < 0.001$) (Table 3). Furthermore, significantly fewer individuals with normal esophageal mucosa or esophagitis consumed salted fat at least once per week and significantly fewer consumed salted fat for at least 6 months per year compared with patients with ESCC (both $P < 0.001$) (Table 3).

Patients with ESCC consumed salted meat significantly more frequently than individuals with normal esophageal mucosa or esophagitis (both $P < 0.001$), with ORs for consumption at least once a week of 2.40 and 6.48, respectively (Table 4). Furthermore, patients with ESCC consumed salted meat for longer

than controls with normal esophageal mucosa or esophagitis cases (both $P < 0.001$). Consuming salted meat for at least 6 months per year increased the risk of ESCC more than 6-fold compared with individuals with normal esophageal mucosa (OR = 6.87), and 44-fold compared with esophagitis cases (OR = 44.38) (both $P < 0.001$) (Table 4). ESCC cases also consumed salted fat significantly more frequently and for longer than individuals with normal esophageal mucosa or esophagitis ($P < 0.001$), with ORs for consumption at least once a week of 7.37 and 5.05, respectively ($P < 0.001$), and ORs for consumption for at least 6 months per year of 85.45 and 74.90, respectively ($P < 0.001$) (Table 4).

Discussion

This study investigated the effects of consuming salted meat and salted fat on the risk of ESCC among individuals with normal esophageal mucosa or esophagitis

Table 3. Consumption of salted meat and salted fat in relation to esophageal diseases.

	Normal (n = 72)	Esophagitis (n = 72)	ESCC (n = 72)	P value*
Intake frequency of salted meat, n (%)				<0.001
<1/month	21 (29.2)	21 (29.6)	10 (13.9)	
<1/week	31 (43.1)	29 (40.8)	17 (23.6)	
≥1/week	20 (27.8)	21 (29.6)	45 (62.5)	
Duration of salted meat intake per year				<0.001
<3 months	42 (58.3)	45 (62.5)	14 (23.3)	
<6 months	25 (34.7)	25 (34.7)	26 (43.3)	
≥6 months	5 (6.9)	2 (2.8)	20 (33.3)	
Intake frequency of salted fat, n (%)				<0.001
<1/month	50 (70.4)	45 (63.4)	22 (30.6)	
<1/week	6 (8.5)	10 (14.1)	10 (13.9)	
≥1/week	15 (21.1)	16 (22.5)	40 (55.6)	
Duration of salted fat intake per year				<0.001
<3 months	56 (78.9)	56 (80.0)	6 (12.5)	
<6 months	10 (14.1)	10 (14.3)	18 (37.5)	
≥6 months	5 (7.0)	4 (5.7)	24 (50.0)	

*Spearman's correlation test. ESCC, esophageal squamous cell carcinoma.

Table 4. Multivariate analysis of characteristics of salted meat consumption and ESCC risk.

	ESCC vs. normal esophageal mucosa			ESCC vs. esophagitis		
	P	OR _{crude} (95%CI)	OR _{adj} (95%CI)*	P	OR _{crude} (95%CI)	OR _{adj} (95%CI)*
Intake frequency of salted meat						
< 1/month	<0.001	1.00	1.00	<0.001	1.00	1.00
1/week		1.15 (0.44–3.00)	0.60 (0.12–2.91)		1.23 (0.47–3.22)	0.63 (0.14–2.81)
≥ 1/week		4.73 (1.89–11.84)	2.40 (0.55–10.43)		4.50 (1.80–11.22)	6.48 (1.65–25.49)
Duration of salted meat intake per year						
< 3 months	<0.001	1.00	1.00	<0.001	1.00	1.00
< 6 months		3.12 (1.38–7.06)	5.78 (1.36–24.64)		3.34 (1.48–7.54)	8.70 (2.07–36.55)
≥ 6 months		12.00 (3.79–37.96)	6.87 (1.25–37.87)		32.14 (6.67–154.85)	44.38 (5.34–368.65)
Intake frequency of salted fat						
< 1/month	<0.001			<0.001		
< 1/week		3.79 (1.22–11.72)	4.50 (0.90–22.50)		2.05 (0.74–5.64)	1.64 (0.35–7.56)
≥ 1/week		6.06 (2.79–13.18)	7.37 (2.53–21.48)		5.11 (2.36–11.07)	5.05 (1.79–14.27)
Duration of salted fat intake per year						
< 3 months	<0.001			<0.001		
< 6 months		16.80 (5.36–52.69)	39.05 (5.71–266.97)		16.80 (5.36–52.69)	19.46 (3.44–110.14)
≥ 6 months		44.80 (12.46–161.05)	85.45 (11.62–628.26)		56.00 (14.48–216.56)	74.90 (11.71–478.95)
Intake length of salted fat per year						
< 3 months	<0.001			<0.001		
< 6 months		16.80 (5.36,52.69)	39.05 (5.71,266.97)		16.80 (5.36,52.69)	19.46 (3.44, 110.14)
≥ 6 months		44.80 (12.46,161.05)	85.45 (11.62,628.26)		56.00 (14.48,216.56)	74.90 (11.71,478.95)

*Further adjusting for age, sex, family EC history, and consumption of fruit, corn, and preserved vegetables. ESCC, esophageal squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

in a high-risk area in China. Among individuals with normal esophageal mucosa, consumption of salted meat and salted fat at least once a week were associated with ORs of ESCC of 2.40 and 7.37, respectively, while consumption for at least 6 months per year were associated with ORs of ESCC of 6.87 and 85.45, respectively. Similarly, among individuals with esophagitis, the ORs of ESCC from consuming salted meat and salted fat at least once a week were 6.48 and 5.05, respectively, and the ORs from consuming them for at least 6 months were 44.38 and 74.90, respectively. Frequent and long-term consumption of salted meat/fat were thus tied to an increased risk of ESCC.

Yanting County is a high-risk area for ESCC in Southwest China. According to the 2008 registry data, the incidence and mortality of EC in this region were 92.81/10⁵ and 77.50/10⁵, respectively.²⁰ More than 80% of the population of Yanting are farmers with a comparatively low economic status and a diet characterized by high consumption of preserved vegetables, salt-processed food, and tuber crops, and low consumption of milk, soy products, and fresh fruit. Salted meat and salted fat are thus typical processed foods commonly consumed in Yanting.

Previous studies from Western countries have reported on the relationship between processed meat and ESCC. Processed meat usually consists of meat items preserved by nitrite/salt treatment, smoking, or fermentation, and includes all types of sausages, bacon, ham, and salted meat.²¹ Studies in Switzerland and Uruguay found significantly increased risks of EC associated with the highest intake category of processed meat.^{22,23} Furthermore, one study in the United States showed significant positive associations between processed meat consumption and ESCC among both black and white men, with ORs increased by 60% and 70%, respectively.²⁴ A previous

study in Yanting also investigated the consumption of salted meat and its interactions with alcohol drinking and tobacco smoking on ESCC.²¹ Although all three groups in the current study had similar smoking and alcohol-drinking habits, salted meat and salted fat consumption were positively associated with the risk of ESCC in individuals with normal esophageal mucosa or esophagitis.

During the preparation of salted meat/fat, fresh meat/fat is preserved in salt for 7 days and then air-dried for 2 months. People in Yanting then eat the salted meat/fat throughout the year. The preparation and storing processes produce N-nitroso compounds, which have been proven to be carcinogenic in animals and possibly in humans.^{25,26} Moreover, salted meat may also contain other carcinogens, such as heterocyclic amines and polycyclic aromatic hydrocarbons, particularly when cooked or processed at high temperatures.²⁷ Fast-food meat products in China contain high levels of heterocyclic amines.²⁸ In addition, salt may directly damage the esophageal mucosa, increasing susceptibility to esophagitis and the risk of EC.²⁶ Processed meat is classified as a Group 1 carcinogen in humans according to the International Agency of Cancer Research: meats prepared with nitrite can produce carcinogenic N-nitroso compounds, while smoking meat produces polycyclic aromatic hydrocarbons, and cooking meat at high temperatures also produces carcinogenic heterocyclic aromatic amines.²⁹

This study was limited by its relatively small sample size. Furthermore, the case-control design may have been subject to recall bias; however, we set individuals with esophagitis as one reference group to reduce this bias. Food intake was less likely to affect health service access in a cancer-specific hospital.

Conclusion

The results of this study suggest that frequent and long-term consumption of salted meat and salted fat increases the risk of ESCC in individuals with normal esophageal mucosa or esophagitis in Yanting County. Health promotion strategies should thus be implemented to help vulnerable people in this region.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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