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Consumption of salt and high-salt foods and the risks of oral, pharyngeal, and oesophageal cancers: the JACC Study

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Abstract

The association between salt and salted food consumption and oral, pharyngeal, and oesophageal cancers remains inconclusive. To address this, we conducted a large-scale nationwide cohort study in Japan, a region globally recognised for its high-salt consumption. In a baseline survey conducted from 1988 to 1990, salt consumption was evaluated using a self-administered food frequency questionnaire in a sample of 42,535 participants aged 40–79 years. Over a median 14.4-year follow-up period, 145 incident cases of oral (n=43), pharyngeal (n=17), and oesophageal (n=85) cancers were observed. A Cox proportional hazards model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) after adjusting for age, sex, smoking status, alcohol consumption, and fruit and vegetable consumption. High-salt consumption was associated with a higher risk of oral, pharyngeal, and oesophageal cancers combined; the multivariable HR for the highest versus lowest tertiles of salt consumption was 1.67 (95% CI: 1.08–2.61, P-trend = 0.01). An excess risk was primarily observed for oral and oesophageal cancers. Among the salt sources, miso soup consumption was positively associated with the combined risk of oral, pharyngeal, and oesophageal cancers; however, the consumption of other high-salt foods was not. In conclusion, high-salt consumption was associated with a higher combined risk of oral, pharyngeal, and oesophageal cancers.

Keywords: Salt consumption; Cancer; Prospective study; General population

List of abbreviations

CI	confidence interval
FFQ	food frequency questionnaire
HR	hazard ratio
JACC	Japan Collaborative Cohort Study for the Evaluation of Cancer Risk

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Introduction

According to the Global Cancer Statistics 2018, oral and pharyngeal cancers rank as the 7th most common cancers worldwide, whereas oesophageal cancer is the 8th most common cancer [1,2]. The incidence of these cancers is on the rise and is projected to increase by 30% for oral and pharyngeal cancers, and by 35% for oesophageal cancer, by 2030 [2,3]. In Japan, the incidence of oral and pharyngeal cancers in males has been reported to be two to three times higher than the global average [4,5] and has increased by 44%, from 6.1 per 100,000 individuals in 2000 to 8.8 per 100,000 individuals in 2015 [6]. A similar trend has been observed in oesophageal cancer [2]. The major risk factors for oral, pharyngeal, and oesophageal cancers are cigarette smoking, alcohol consumption, and infections such as human papillomavirus [1,2].

The oral cavity, pharynx, and oesophagus are parts of the digestive tract that extend into the stomach. Their surfaces are lined with the mucosal epithelium of non-keratogenic stratified squamous cells, and approximately 90% of cancers in these organs are squamous cell carcinomas [2,3,7]. These similarities suggest that oral, pharyngeal, and oesophageal cancers share common dietary risk factors, such as a high consumption of salt, red meat, and processed meat and a low consumption of vitamin C [8-10]. The underlying mechanism for the association between high-salt consumption and the risk of oral and oesophageal cancers is likely an inflammatory response induced by high-salt concentrations [11,12]. Chronic inflammation leads to elevated levels of chemical mediators, such as tumour necrosis factor α (TNF-α) and transforming growth factor β (TGF-β), which cause oxidative stress, DNA damage, and subsequent squamous cell carcinoma [13,14].

According to a meta-analysis of 16 case-control studies and 2 cohort studies, salt or salted food consumption is positively associated with the risk of oesophageal cancer [15]. However, these two cohort studies did not show any significant associations [16,17]. No cohort study has definitively reported an association between salt or high-salt food consumption and the risk of oral or pharyngeal cancer. Furthermore, only one case-control study [18] has examined the dose-response relationship between salt consumption and estimated the risk of oesophageal cancer using a validated food frequency questionnaire.

Herein, we examined the dose-response relationships between salt and high-salt food consumption and the risk of oral, pharyngeal, and oesophageal cancers in a large prospective cohort study of middle-aged Japanese individuals.

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Experimental methods

Study cohort

The Japan Collaborative Cohort Study for the Evaluation of Cancer Risk (JACC Study) is a large nationwide community-based prospective study conducted using a baseline survey from 1988 to 1990 across 45 administrative districts in Japan. A total of 110,585 participants (46,395 men and 64,190 women) aged 40–79 years completed self-administered questionnaires on lifestyle and medical histories related to cancer and cardiovascular disease. The details of this study have been described previously [19, 20]. Using the population-based cancer registry, follow-up for cancer incidence was conducted in 24 areas until the end of 2009 in four areas: 2008 in two areas, 2006 in two areas, 2003 in one area, 2002 in eight areas, 2000 in one area, 1999 in one area, 1997 in four areas, and 1994 in one area.

Of the initial 110,585 participants, we excluded 50,158 individuals from three areas where the dietary questionnaire survey regarding salt consumption was not conducted and 21 areas where surveillance for cancer incidence was not conducted. Of the remaining 60,427 participants, 43,215 provided valid responses to the dietary questionnaire and were enrolled in the study. Finally, 680 additional participants with a history of cancer were excluded, and 42,535 participants were included in the analysis.

This study was conducted according to the guidelines laid down in the Declaration of The Ethical Board of Hokkaido University (approval number 14–044) and Osaka University (approval number 14285) approved the Helsinki Declaration and all procedures involving human subjects. Individual informed consent was obtained from 36 of the 45 study areas (written consent in 35 and oral consent in one area), and group consent from the area leader was obtained from the remaining nine areas.

Cancer assessment and follow-up

Of the 24 survey areas for cancer incidence, 10 were combined because of their geological similarities. Cancer incidence was determined using population-based cancer registries, supported by a systematic review of hospital-based cancer registries in 11 areas and direct hospital-based cancer registries in the remaining four areas. The mortality-to-incidence ratios were 0.31 to 0.61 in males and 0.15 to 0.53 in females, based on population-based cancer registries, and 0.25 to 0.72 in males and 0.13 to 0.79 in females, based on hospital-based cancer registries or inpatient records. The mortality-to-incidence ratios of the total area were 0.43 in males and 0.38 in females [21]. Three areas had a mortality-to-incidence ratio > 0.50

(exceeding the international accuracy standard [22]) for both sexes, accounting for only 12% of the total participants in the present study. In the subsample analysis of cancer cases with stage information (1: in situ, 2: localised, 3: regional lymph node involvement, 4: regional tissue or organ involvement, and 5:metastasis), we examined the association between salt consumption and the combined risk of oral, pharyngeal, and oesophageal cancers stratified by the presence or absence of advancement (1–2 and 3–5, respectively).

The dates and causes of death were verified annually or biannually with permission from the Director-General of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post, and Telecommunications) and/or the Ministry of Health, Labour, and Welfare, Japan. The incidence data were coded according to the International Classification of Diseases, Revision 10 (ICD 10). Specifically, we defined oral (C01–C06 and C09), pharyngeal (C10 and C12-C14), and oesophageal (C15) cancers. Those registered as having cancer for the second or subsequent time were also included in the analysis.

Dietary assessment

Participants were asked to complete a 35-item food frequency questionnaire (FFQ) to determine their dietary consumption patterns. For 33 of the food items, the following five options were available: “rarely”, “1 to 2 days per month”, “1 to 2 days per week”, “3 to 4 days per week”, and “almost every day”. For miso (salty soybean paste) soup consumption, participants could choose one of the four options: “rarely”, “a few times per month”, “almost every other day”, and “every day”. Participants who chose “every day” were further asked to specify the number of bowl servings per day.

In our analysis, the following foods were regarded as high-salt foods, with a salt content of 1.0 g or more per 100 g of food weight, based on the Standard Tables of Food Composition, Fifth Revised Edition: These included miso soup, dried and salted fish, processed meat, fish (ham and fish paste), and salty pickles. The average daily consumption of nutrients and total energy was calculated by multiplying the consumption frequency of each food item by its nutrient content and energy per serving, and then adding the nutrient consumption for all food items. The energy-adjusted nutrient consumption was calculated using the residual method. The validity of this FFQ has been previously reported, using a 12-day weighed dietary record as a reference [20]. Spearman’s rank correlation coefficient was 0.31 for salt, 0.72 for miso soup, 0.59 for boiled beans, 0.52 for deep-fried foods, 0.46 for fried vegetables, 0.46 for dried and salted fish, 0.67 for ham, 0.57 for fish paste, and 0.68 for salty pickles. The estimated mean salt consumption in the validation study was 4.0 g/day based on the FFQ and 10.6 g/day based on dietary records [20].

Statistical analysis

Person-years of follow-up were calculated as the duration from the date of the baseline questionnaire to the occurrence of cancer, death, moving out of the study area, or the end of follow-up, whichever occurred first. Age- and sex-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for oral, pharyngeal, and oesophageal cancers were calculated using Cox proportional hazards regression models according to the tertiles and 1 g increment of salt consumption. To examine the dose-response relationship, we used restricted cubic splines to model the nonlinear effects, with three knots placed at the medians of the tertiles of salt consumption after adjustment for age and sex.

In the multivariable analysis, smoking status (never and ever smokers) and alcohol consumption (never and ever drinkers) were adjusted for oral and oesophageal cancers (model 1). Further adjustments for fruit and vegetable consumption (tertiles for each) were conducted for oral, pharyngeal, and oesophageal cancers (Model 2). P-values for linear trends were calculated by treating the median salt consumption in each tertile. The interaction between salt consumption and smoking or alcohol consumption was assessed using an interaction term generated by multiplying the median of each salt consumption tertile by smoking status and alcohol consumption. The Cox proportional hazards model confirmed the assumptions of the Schoenfeld residual test.

All statistical analyses were performed using SAS statistical package, V.9.4 (SAS Institute). All probability values for the statistical tests were two-tailed. Statistical significance was defined as a P-value ≤ 0.05, and a P-interaction ≤ 0.10.

Results

During a median follow-up period of 14.4 years (568,342 person-years), we documented 145 total patients with cancer, including 43, 17, and 85 patients with oral cancer, pharyngeal cancer, and oesophageal cancer, respectively. Table 1 shows the participants' characteristics according to the salt consumption tertiles. Participants with higher salt consumption were older, more likely to be male, and consumed higher amounts of vegetables.

Table 2 shows the HRs and 95% CIs according to tertiles of consumption and 1 g increments of salt consumption. High-salt consumption was associated with a higher risk of

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developing oral and oesophageal cancers, but not pharyngeal cancer. The multivariable HR (95% CI) for the highest versus lowest tertiles of salt consumption (model 1) was 1.63 (1.05–2.52, P-trend=0.01) for oral, pharyngeal, and oesophageal cancers combined, 1.79 (0.83–3.86, P-trend=0.01) for oral cancer, and 2.04 (1.09–3.80, P-trend=0.05) for oesophageal cancer. After further adjustment for fruit and vegetable consumption (model 2), the multivariable HR (95% CI) was 1.67 (1.08–2.61, P-trend=0.01) for oral, pharyngeal, and oesophageal cancers combined. The multivariable HR (95% CI) per 1 g increment of salt consumption was 1.33 (1.07-1.65) for oral, pharyngeal, and oesophageal cancers combined (model 2), 1.51 (1.00-2.29) for oral cancer (model 1), and 1.38 (1.04-1.84) for oesophageal cancer (model 1). A dose-response relationship was confirmed by the spline curve shown in Supplemental Figure 1. In the subsample analysis of cancers with stage information (No. of cases = 55), salt consumption tended to be associated with the combined risk of oral, pharyngeal, and oesophageal cancers in advanced cases but not in non-advanced cases, although the interaction was not statistically significant (Supplemental Table 1).

When stratified by smoking status and alcohol consumption, the positive association between salt consumption and the combined risk of oral, pharyngeal, and oesophageal cancers did not vary between never and ever smokers (P-interaction = 0.56, model 1, and 0.86 in model 2) nor between never and ever drinkers (P-interaction = 0.77, model 1 and 0.87, model 2) (Table 3).

Table 4 shows the association between salted food consumption and the combined risk of oral, pharyngeal, and oesophageal cancers. Miso soup consumption of two or more cups/day was associated with a higher risk than consumption of less than one cup/day; however, the consumption of other high-salt foods had no significant association.

Discussion

In this cohort study of Japanese adults, we first observed that salt consumption was positively associated with the combined risk of oral, pharyngeal, and oesophageal cancers, particularly oral and oesophageal cancers. Among high-salt foods, miso soup, a significant source of dietary salt in Japan, is positively associated with cancer risk.

The association between total salt consumption and gastric cancer has been examined in many cohort studies [23]; however, investigations into the relationship between salt consumption and oral, pharyngeal, and oesophageal cancers are limited. A meta-analysis of 16 case-control studies and two cohort studies that examined the association of salt or salted food consumption with oesophageal cancer risk reported a summary odds ratio (95% CI) for high versus low consumption groups of 1.97 (1.49–2.61) in case-control studies and 1.04 (1.00–1.08) in cohort studies. [15] Two cohort studies were conducted in Japan [16] and the United States. [17] A previous 13.9-year cohort study of Japanese male and female aged 30 to 79 years demonstrated no association between salted food consumption and the risk of oesophageal cancer; the multivariable HR (95% CI) was 1.55 (0.18–6.39) in male and 1.22 (0.35–5.43) in female for high versus low consumption of salted food [16]. A 9.7-year cohort study of 494,968 American male and female aged 51 to 70 years reported no elevated risks of oesophageal squamous cell carcinoma and adenocarcinoma associated with one score increment of sodium consumption; the multivariable HR (95% CI) was 0.96 (0.93-0.99) and 0.99 (097-1.01), respectively [17]. Our findings confirmed a positive association between salt consumption and the risk of oral and oesophageal cancers, as observed in gastric cancer.

Several studies have examined the association between high-salt foods and the risk of oesophageal and gastric cancer; however, few studies have been conducted on oral and pharyngeal cancers. A greater consumption of processed meat was found to be associated with a higher risk of oesophageal and gastric cancers in meta-analyses of observational studies [23,24] and with a higher risk of oral cancer in a case-control study [25]. However, other high-salt foods have not been consistently associated with the risk of these cancers. Positive associations with pickled foods have been observed in gastric cancer [23] but not in oesophageal cancer [24]. Similarly, no positive association between salted fish consumption and gastric cancer has been reported [23]. Miso soup consumption was not associated with the risk of oral cancer in a Japanese case-control study [26] or gastric cancer in a meta-analysis [23]. Further investigation is required to confirm whether high-salt foods are associated with an increased risk of oral, pharyngeal, and oesophageal cancers.

A positive association with the risk of oral, pharyngeal, and oesophageal cancers was primarily observed for miso soup, probably because of the larger variation in salt consumption across its categories compared to other high-salt foods. Additionally, considering that miso soup is usually served hot, high temperatures may increase the risk of oral, pharyngeal, and oesophageal cancers [27-29].

Our study had two strengths. First, it was a long-term cohort study that included many participants. Second, the participants were recruited from the general Japanese population, which may increase the generalisability of our findings. This study has a few limitations that should be considered when interpreting our findings and warrant further investigation. First, salt consumption estimated using the FFQ was underestimated. Consequently, our findings should be interpreted carefully based on absolute salt consumption levels. However, the relative consumption level showed moderate validity compared to the dietary record, as shown in the Experimental methods [20], and the findings comparing the lowest and highest categories were less likely to be affected by this underestimation. If the underestimation was not biased towards the outcome, random errors in the exposure level could have diluted the true association. Second, we had a low statistical power owing to the small number of pharyngeal cancer cases; therefore, we did not find a significant association between salt consumption and the risk of pharyngeal cancer. Third, we did not examine chemical mediators to interpret the relationship between salt consumption and the risks of oral, pharyngeal, and oesophageal cancers.

In conclusion, high-salt consumption was associated with a higher combined risk of oral, pharyngeal, and oesophageal cancers. However, further epidemiological and biological studies are required to confirm these findings.

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Declaration of interests

The authors declare none.

Authorship

K. O., E. S. E, S. T., M. I., and H. I.: Conceptualised and conducted the study. A. T. Data curation. K. O., E. S. E, S. T., M. I., K. R. and H. I.: Methodology. K.O.: Formal Analysis and writing the original draft. All authors contributed to the analytical strategy and interpretation of the results, critically reviewed the manuscript for important intellectual content, approved the final version for publication, and agreed to be accountable for all aspects of the study.

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Table 1. Risk characteristics according to tertiles of salt consumption

	Tertiles of salt consumption		
	Low	Middle	High
No. of participants	14,178	14,179	14,178
Median salt consumption, g/day (IQR)	3.2 (2.6-3.6)	4.8 (4.4-5.2)	6.7 (6.1-7.4)
Mean age, y (SD)	55.5 (9.6)	56.3 (10.0)	57.7 (10.2)
Men, n (%)	4,875 (34.4)	5,109 (36.0)	6,548 (46.2)
Mean body mass index, kg/m^2 (SD)	22.8 (3.0)	22.7 (2.9)	22.8 (3.0)
Smoking status			
Never smokers, n (%)	8,819 (62.2)	8,931 (63.0)	8,268 (58.3)
Past smokers, n (%)	1,437 (10.1)	1,577 (11.1)	1,704 (12.0)
Current smokers, n (%)	3,096 (21.8)	2,928 (20.7)	3,521 (24.8)
Alcohol consumption			
Never drinkers, n (%)	7,105 (50.1)	7,417 (52.3)	7,180 (50.6)
Past drinkers, n (%)	372 (2.6)	483 (3.4)	629 (4.4)
Current drinkers, n (%)	6,412 (45.2)	5,901 (41.6)	6,024 (42.5)
Median fruit consumption, g/day (IQR)	81 (34-127)	88 (50-161)	88 (50-161)
Median vegetable consumption, g/day (IQR)	80 (50-146)	99 (59-740)	110 (67-759)

IQR, interquartile range; SD, standard deviation

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Table 2. Hazard ratios (95% confidence intervals) of oral, pharyngeal, and oesophageal cancers according to tertiles and 1 g increment of salt consumption

	Tertiles of salt consumption				Per 1g increment
	Low	Middle	High	P-trend	
No. of participants	14,178	14,179	14,178		42,535
Person-years	161,459	190,827	216,056		568,342
Oral, pharyngeal, and oesophageal cancers					
No. of cases	28	38	79		145
Age and sex-adjusted HR	Ref	1.06 (0.65-1.73)	1.56 (1.01-2.41)	0.02	1.28 (1.03-1.59)
Multivariable HR (Model 1)	Ref	1.07 (0.66-1.75)	1.63 (1.05-2.52)	0.01	1.31 (1.06-1.63)
Multivariable HR (Model 2)	Ref	1.10 (0.67-1.80)	1.67 (1.08-2.61)	0.01	1.33 (1.07-1.65)
Oral cancer					
No. of cases	9	7	27		43
Age and sex-adjusted HR	Ref	0.61 (0.23-1.63)	1.80 (0.84-3.88)	0.05	1.52 (1.00-2.30)
Multivariable HR (Model 1)	Ref	0.60 (0.22-1.62)	1.79 (0.83-3.86)	0.01	1.51 (1.00-2.29)
Pharyngeal cancer					
No. of cases	6	4	7		17
Age and sex-adjusted HR	Ref	0.48 (0.14-1.71)	0.53 (0.17-1.61)	0.30	0.74 (0.41-1.32)
Oesophageal cancer					
No. of cases	13	27	45		85
Age and sex-adjusted HR	Ref	1.65 (0.85-3.19)	1.90 (1.02-3.55)	0.05	1.33 (1.00-1.77)
Multivariable HR (Model 1)	Ref	1.68 (0.86-3.26)	2.04 (1.09-3.80)	0.05	1.38 (1.04-1.84)

Model 1: adjusted for age, sex, smoking status, and alcohol consumption.
Model 2: adjusted further for fruit and vegetable consumption.
HR hazard ratio

Table 3. Hazard ratios (95% confidence intervals) of oral, pharyngeal, and oesophageal cancers combined according to tertiles of salt consumption, stratified by smoking and drinking status

	Tertiles of salt consumption			P- trend	P-interaction
	Low	Middle	High		
Smoking status					
Never smokers					
No. of participants	8,819	8,831	8,268		
Person-years	101,101	122,471	130,418		
No. of cases	9	10	23		
Age and sex-adjusted HR	Ref	0.82 (0.33-2.02)	1.42 (0.65-3.11)	0.27	
Multivariable HR (Model 1)	Ref	0.82 (0.33-2.03)	1.44 (0.66-3.16)	0.12	
Multivariable HR (Model 2)	Ref	0.86 (0.35-2.14)	1.60 (0.71-3.60)	0.16	
Ever smokers					
No. of participants	4,533	4,505	5,225		
Person-years	52,613	59,584	75,504		
No. of cases	19	28	54		
Age and sex-adjusted HR	Ref	1.19 (0.66-2.13)	1.61 (0.95-2.74)	0.06	
Multivariable HR (Model 1)	Ref	1.20 (0.67-2.15)	1.65 (0.97-2.80)	0.09	0.56
Multivariable HR (Model 2)	Ref	1.22 (0.67-2.19)	1.62 (0.94-2.79)	0.08	0.86
Alcohol consumption					
Never drinkers					
No. of participants	6,734	7,104	6,941		
Person-years	80,907	99,697	110,971		
No. of cases	6	8	21		
Age and sex-adjusted HR	Ref	0.95 (0.33-2.73)	1.82 (0.72-4.57)	0.12	
Multivariable HR (Model 1)	Ref	0.95 (0.33-2.74)	1.83 (0.73-4.60)	0.12	
Multivariable HR (Model 2)	Ref	0.93 (0.32-2.71)	1.73 (0.67-4.47)	0.16	
Ever drinkers					
No. of participants	6,481	6,148	6,372		
Person-years	77,431	86,018	99,512		
No. of cases	22	30	56		
Age and sex-adjusted HR	Ref	1.10 (0.64-1.92)	1.45 (0.88-2.39)	0.11	
Multivariable HR (Model 1)	Ref	1.11 (0.64-1.92)	1.49 (0.90-2.45)	0.09	0.77
Multivariable HR (Model 2)	Ref	1.14 (0.66-2.00)	1.53 (0.92-2.55)	0.08	0.87

Model 1: adjusted for age, sex, smoking status, and alcohol consumption.

Model 2: adjusted further for fruit and vegetable consumption.

In the stratified analysis by smoking status and alcohol consumption, the stratified variables were not included for adjustment.

HR hazard ratio

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Table 4. Hazard ratio (95% confidence intervals) of oral, pharyngeal, and oesophageal cancers combined according to the frequency of high-salt foods

	Median salt consumption (g/day)	No. of participants	Person-years	No. of cases	Age and sex-adjusted HR	Multivariable HR (Model 1)	Multivariable HR (Model 2)
Miso soup							
<1 cup/day	3.8	12,243	134,124	19	Ref	Ref	Ref
1 cup/day	4.3	11,290	142,078	19	0.86 (0.46-1.63)	0.87 (0.46-1.64)	0.84 (0.44-1.59)
2 cups /day	5.8	11,707	178,567	52	1.71 (1.01-2.90)	1.72 (1.01-2.92)	1.63 (0.95-2.81)
3+ cups/day	7.3	7,295	113,574	55	2.22 (1.31-3.77)	2.24 (1.32-3.81)	2.27 (1.33-3.86)
P-trend					< 0.001	< 0.001	0.001
Dried and salted fish							
<1 times/week	4.3	16,020	196,240	50	Ref	Ref	Ref
1-2 times/week	4.9	15,987	223,249	58	1.02 (0.70-1.49)	1.02 (0.70-1.49)	1.03 (0.71-1.51)
3+ times/week	5.5	9,940	142,751	36	0.97 (0.63-1.49)	0.97 (0.63-1.49)	0.99 (0.64-1.52)
P-trend					0.90	0.91	0.10
Processed meat and fish							
<1 times/week	4.4	13,961	179,579	51	Ref	Ref	Ref
1-2 times/week	4.7	15,894	212,054	49	0.91 (0.62-1.35)	0.92 (0.62-1.36)	0.94 (0.63-1.39)
3+ times/week	5.1	8,671	117,079	23	0.78 (0.48-1.27)	0.79 (0.48-1.30)	0.82 (0.49-1.35)
P-trend					0.32	0.36	0.43
Salty pickles							
<1 times/week	3.8	4,829	58,550	17	Ref	Ref	Ref
1-2 times/week	4.1	5,372	69,068	18	0.92 (0.47-1.78)	0.88 (0.46-1.71)	0.90 (0.46-1.75)
3+ times/week	5.0	31,945	435,689	109	0.91 (0.55-1.52)	0.88 (0.52-1.46)	0.93 (0.55-1.55)
p-trend					0.75	0.64	0.83

Model 1: adjusted for age, sex, smoking status, and alcohol consumption.
Model 2: adjusted further for fruit and vegetable consumption.
HR hazard ratio

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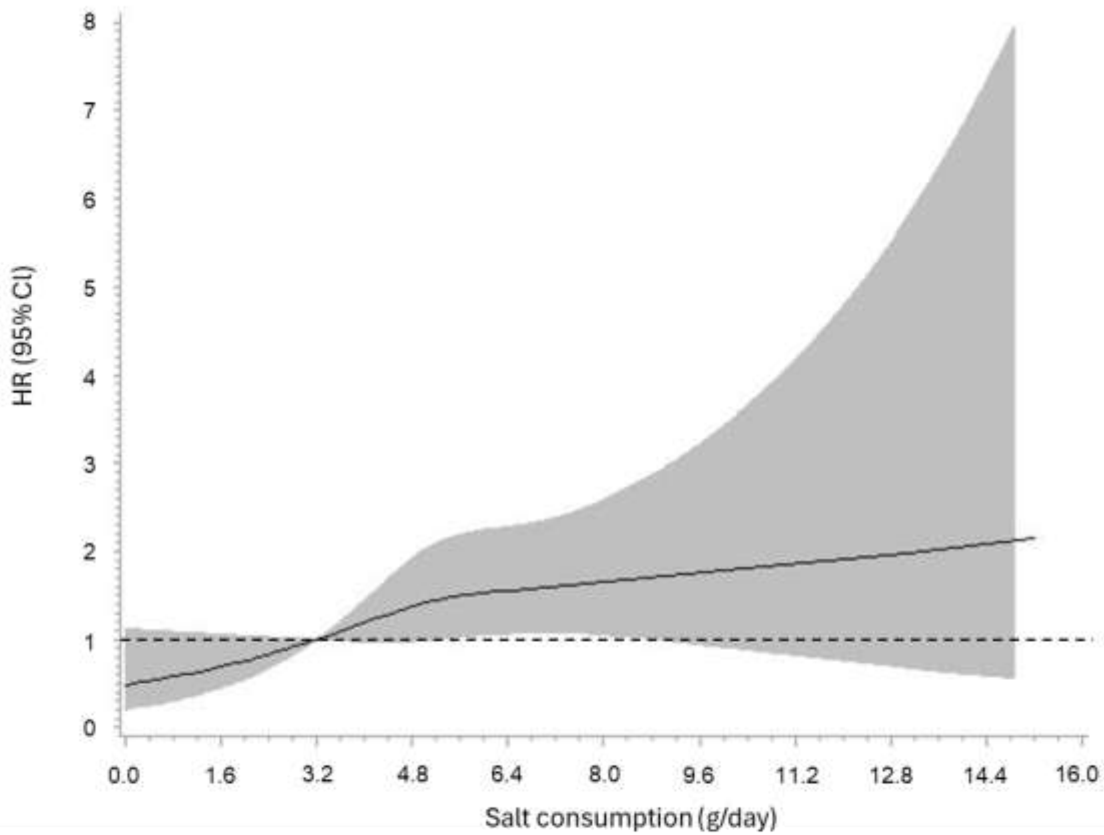

Supplemental Figure 1

The restricted cubic spline of the association between salt consumption and the combined risk of oral, pharyngeal, and oesophageal cancers after adjustment for age and sex. Knots were placed at the medians of salt consumption tertiles. The black line and shaded area represent the HR and 95%CI.

Supplemental Table 1. Hazard ratios (95% confidence intervals) of oral, pharyngeal, and oesophageal cancers combined according to the absence or presence of advancement

	Tertiles of salt consumption			P- trend	P -interaction
	Low	Middle	High		
Absence of advancement (1 to 2)					
No. of participants	227	269	348		
Person-years	1,845	2,415	3,527		
No. of cases	7	8	12		
Age and sex-adjusted HR	Ref	0.81 (0.29-2.26)	0.72 (0.28-1.86)	0.50	
Multivariable HR (Model 1)	Ref	0.81 (0.29-2.25)	0.73 (0.28-1.89)	0.53	
Multivariable HR (Model 2)	Ref	0.86 (0.31-2.42)	0.78 (0.30-2.04)	0.61	
Absence of advancement (3 to 5)					
No. of participants	130	176	243		
Person-years	1,162	1,724	2,869		
No. of cases	3	10	15		
Age and sex-adjusted HR	Ref	1.79 (0.49-6.57)	1.33 (0.38-4.66)	0.94	
Multivariable HR (Model 1)	Ref	1.81 (0.48-6.80)	1.37 (0.39-4.85)	0.90	0.37
Multivariable HR (Model 2)	Ref	1.88 (0.50-7.14)	1.40 (0.40-4.99)	0.85	0.47

Model 1: adjusted for age, sex, smoking status, and alcohol consumption.

Model 2: adjusted further for fruit and vegetable consumption.

HR hazard ratio

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