Original Article

Prospective cohort study evaluating the relationship between salted food intake and gastrointestinal tract cancer mortality in Japan

Atsuhiko Murata MD[1], Yoshihisa Fujino PhD[1], Truong-Minh Pham PhD[1], Tatsuhiko Kubo PhD[1], Tetsuya Mizoue PhD[2], Noritaka Tokui PhD[3], Shinya Matsuda PhD[1], Takesumi Yoshimura PhD[4]

[1]*Department of Preventive Medicine and Community Health, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan*
[2]*Department of Epidemiology, Research Institute, International Medical Center of Japan, Tokyo, Japan*
[3]*Department of Preventive Medicine and Dietetics, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan*
[4]*Fukuoka Institute of Health and Environmental Sciences, Fukuoka, Japan*

Purpose: To investigate whether a high salted food intake increases the risk of gastrointestinal tract cancer mortality. Methods: We conducted a prospective study of 6830 Japanese inhabitants to evaluate the association between salted food consumption and the risk of gastrointestinal tract cancer mortality. Data were obtained from a prospective cohort study in Japan. Salted food consumption, determined from a baseline questionnaire, was classified into the two categories of 'low intake' and 'high intake'. The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CI). Findings: Total of 174 gastrointestinal tract cancer deaths (47 esophagus cancer, 87 stomach cancer, 23 colon cancer and 17 rectal cancer) were observed during 94996 person-years of follow-up, with a mean follow-up period of 8.9 years. After adjustment for age, body mass index, physical activity, smoking, alcohol, history of diabetes mellitus and dietary items, including vegetables, fruit, tea, red meat and processed meat, the HR for stomach cancer in males with high salt intake was 2.05 (95% CI:1.25 - 3.38) whereas that of rectal cancer was 3.58 (95% CI: 1.08 - 11.89). In contrast, no association was seen in females. Further, no association was seen between higher salted food consumption and esophagus and colon cancer in either sex. Conclusions: A significant association was seen between higher salted food consumption and stomach and rectal cancer mortality in men, but not in women. No association was seen between higher consumption and esophagus and colon cancer mortality in either men or women.

Key Words: prospective cohort study, gastrointestinal tract cancer, diet, mortality, salted food

INTRODUCTION

Gastrointestinal tract cancer, from the esophagus to the rectum, remains one of the most common cancers and causes of cancer death worldwide in both men and women.[1-3] Although medical and surgical treatments such as endoscopic therapy, radiotherapy, operation and adjuvant chemotherapy have markedly improved the prognosis of patients with gastrointestinal tract cancer,[4-6] the mortality still remains high.[1-3]

Many researchers have investigated the association between dietary patterns and gastrointestinal tract cancer incidence or mortality, and a number of studies have indicated that the high incidence of gastrointestinal tract cancer might be associated with changes in dietary habits, such as Westernization of the diet.[7-9] Furthermore, several population-based case-control and cohort studies have suggested that important components of the diet, such as alcohol, processed meat and red meat, have an unfavorable effect on the risk of gastrointestinal tract cancer.[10-11]

With regard to salted foods, some studies have reported that a high intake of salted foods increases the risk of several pathological conditions such as asthma, renal calcium stones and osteoporosis.[12-13] In particular, a strong association between a high intake of some salted foods and an increased risk of hypertension or cardiovascular disease has been reported.[14-15] The World Health Organization has therefore recommended that overall consumption of salt-preserved foods and salt should be moderated so as to lower the risk of these diseases.[16]

Corresponding Author: Dr Atsuhiko Murata, Department of Preventive Medicine and Community Health, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu-City 807-8555, Japan.
Tel: +81-93-691-7244; Fax: +81-93-603-4307
Email: amurata@med.uoeh-u.ac.jp; evergreenh201@qtnet.ne.jp
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However, little information is available on the relationship between salted food intake and gastrointestinal tract cancer mortality in prospective cohort studies. If a high intake of salted foods influences the risk of gastrointestinal tract cancer mortality, the findings would generate useful knowledge for the epidemiology of cancer, and have significant implications for public health or nutrition. To better understand the relationship between salted food intake and gastrointestinal cancer, we conducted a prospective study based on a population-based cohort study in Japan to investigate whether a high intake of salted food increased the risk of gastrointestinal tract cancer mortality.

MATERIALS AND METHODS

Study population

Study subjects were participants of the Miyako Study, a cohort study conducted in three areas of Fukuoka Prefecture, Japan. Details of the present cohort study have been described in our previous reports.[17-19] The baseline survey was conducted from 1986 to 1989 via invitations to all inhabitants aged 30 to 79 years living in town A, village B, and selected districts of city C (9719 subjects in total) to participate in a self-administrated questionnaire survey. The response rate was 84.1%, comprising 8172 subjects (3605 men and 4567 women), who constituted the cohort. Baseline characteristics were obtained through self-administrated questionnaires, which included questions on health-related factors including smoking, alcohol, disease history and other factors.

The 8172 subjects were then followed for vital status, which was updated annually with the collaboration of the respective municipal offices, until the end of 1999 in one of the study areas and until the end of 2003 in the other two. The underlying cause of deaths occurring during the study period was ascertained from death certificates and coded according to the International Classification of Disease and Injuries, 9th version (ICD-9). In the present analysis, esophagus, stomach, colon and rectal cancer were defined as code 150, 151, 153, and 154 in the ICD-9, respectively.

The research protocol was approved by the Ethics Committee of Medical Care and Research of the University of Occupational and Environmental Health, Kitakyushu, Japan.

Exposure assessment

The usual intake of salted food during the year preceding the start of the study was assessed from the self-administrated questionnaire, which included an item on salted food intake. Salted food intake was assessed at the five levels of 'twice or more per day', 'once a day ', '2 - 4 times per week', '2 - 4 times per month' and 'seldom or never'. For the present analysis, consumption levels were converted into two groups by combining the '2 - 4 times per month' and 'seldom or never' groups into a new 'low intake' group, and the 'twice or more per day', 'once a day' and '2 - 4 times per week' groups into a 'high intake' group.

Exclusion

For the present analysis, we excluded 739 subjects aged younger than age 40 years and 110 with any cancer diagnosed before the study baseline and then 493 with missing information on salted food consumption. Finally, the analysis was conducted in 6830 subjects (3074 men and 3756 women).

Statistical analysis

Baseline characteristics of the study subjects in the two salt intake groups were compared using the chi-square test for categorical variables and ANOVA for continuous variables. We counted the number of person-years of follow-up for each subject from baseline until the date of death, the date of migration from the study area or the end of follow-up, whichever came first. We used Cox proportional hazards regression analysis to estimate hazard ratios (HRs) and their 95% confidence intervals (CI) for gastrointestinal tract cancer mortality according to the category of salted food consumption by gender, with the 'low intake' group considered the reference group. Patterns in Schoenfeld residuals with time were considered to identify possible violation of the proportional hazards model, and showed that our analysis was valid.[20]

In addition to age and body mass index (BMI), the following variables were considered as potential confounders and included in the proportional hazards model (all missing data were considered an additional category, termed the 'unknown category', and included in the analysis): physical activity (no exercise, light exercise, heavy exercise), smoking (never smoker, ex-smoker and current smoker), alcohol (never drinker, ex-drinker and current drinker) and history of diabetes (yes or no). In the additional model, we adjusted for the above confounding factors and also for intake of other food items including vegetables, fruit, tea, red meat and processed meat, because some previous reports suggested that these items had a possible influence on the risk of gastrointestinal cancer.[7-11] In particular, we estimated HRs for the associations between salted food and gastrointestinal cancer mortality, taking into account only the effect of vegetables, as several previous studies have suggested that some vegetables were preserved by salting, and thus a higher consumption of vegetables may be associated with high salt intake.[21-22] Intake of these food items was categorized into two groups, namely 'daily intake' and 'non-daily intake'.

All p values and 95 % CI presented were based on two-sided tests. A value of $p < 0.05$ was considered significant. All statistical analyses were performed using the STATA statistical software package version 9.0 (Stata Corporation, College Station, TX, USA).

RESULTS

As shown in Table 1, during 94996 person-years of follow-up in 6830 subjects (average follow-up 13.9 years), 174 deaths from gastrointestinal tract cancer were recorded, including 47 cases of esophagus cancer, 87 of stomach cancer, 23 of colon cancer and 17 of rectal cancer. The mean follow-up period for these cancer cases was 8.9 years. Mean age at study baseline was 50.8 years. With regard to daily food intake of the cohort, high consumption of vegetables, fruit and tea (32.3%, 55.9%, and 43.9%, respectively) and low consumption of red and processed meat (8.5% and 5.7%, respectively) was observed.

Table 1. Baseline characteristics of subjects in this cohort

Variables	Number	Rate (%)
Number of subjects	6830	
Persons-years of follow up	94996	
Number of each cancer		
Esophagus	47	
Stomach	87	
Colon	23	
Rectum	17	
Mean age (year)	50.8	
SD	12.9	
Mean BMI (kg/m^2)	22.8	
SD	3.1	
Physical activity		
No exercise	2437	35.7
Light exercise	3301	48.3
Heavy exercise	974	14.3
Unknown	118	1.7
Smoking		
Never smokers	3403	49.8
Ex-smokers	974	14.3
Current smokers	1838	26.9
Unknown	615	9
Alcohol		
Never drinkers	1626	23.8
Ex-drinkers	110	1.6
Current drinkers	4488	65.7
Unknown	606	8.9
History of diabetes mellitus	271	4
Daily intake of vegetables	2206	32.3
Daily intake of fruit	3816	55.9
Daily intake of tea	2998	43.9
Daily intake of red meat	579	8.5
Daily intake of processed meat	387	5.7

†SD indicates standard deviation. BMI indicates body mass index.

Comparison of characteristics of subjects by level of salted food intake is shown in Table 2. Subjects with a high intake of salted food tended to be older in both sexes. In males, smoking and alcohol habits, history of diabetes mellitus, and daily intake of vegetables and processed meat differed between the two salted food intake groups (p <0.05). In females, alcohol habits and daily intake of vegetables, red meat and processed meat and differed between the two salted food intake groups (p <0.05).

Multivariable-adjusted HRs and 95% CI for gastrointestinal tract cancer mortality by salted food intake are presented in Table 3. After adjustment for age, BMI, physical activity, smoking, alcohol intake, history of diabetes mellitus, and intake of other foods including vegetables, fruit, tea, red meat and processed meat, no significant association between high salted food intake and esophagus cancer mortality was seen in males or females (HR 1.55, 95% CI: 0.18 - 6.39 and 1.22, 95% CI: 0.35 - 5.43, respectively). In contrast, a significant association between higher salted food consumption and increased stomach cancer mortality was revealed in males (HR 2.05, 95% CI: 1.25 - 3.38), but not in females (HR 1.93, 95%

Table 2. Comparison of characteristics of subjects according to salted food and sex

	Males (n =3074)			Females (n = 3756)		
	Low intake	High intake	*p* value	Low intake	High intake	*p* value
Number of subjects	1246	1828		1221	2535	
Persons-years of follow up	16880	24766		17343	36007	
Number of each cancer						
Esophagus	12	14		8	13	
Stomach	30	37		8	12	
Colon	9	7		3	4	
Rectum	3	8		5	1	
Mean age (year)	49.6	51.3	<0.001	50.2	51.3	0.016
SD	12.3	12.8		12.6	13.3	
Mean BMI (kg/m^2)	22.8	22.9	0.351	22.6	22.8	0.161
SD	2.8	2.9		3.1	3.3	
Physical activity (%)						
No exercise	40.3	45.2	0.202	27.3	30.6	0.401
Light exercise	42.7	34.3		51.5	59.7	
Heavy exercise	15.9	17.8		19.7	8.3	
Unknown	1.1	2.7		1.5	1.4	
Smoking (%)						
Never smokers	15.7	21.6	<0.001	73.2	75.7	0.1
Ex-smokers	24.6	28.5		4.5	3.6	
Current smokers	55.2	47.4		8.9	6.9	
Unknown	4.5	2.5		13.4	13.8	
Alcohol (%)						
Never drinkers	7.6	11.3	<0.001	31.9	36.9	0.044
Ex-drinkers	1.7	2.7		1.6	0.8	
Current drinkers	88	82.2		52.1	49.4	
Unknown	2.7	3.8		14.4	12.9	
History of diabetes mellitus (%)	4.7	6.6	0.018	2.1	2.6	0.413
Daily intake of vegetables (%)	26.6	24.8	0.026	41	36.3	<0.001
Daily intake of fruit (%)	42.9	41.6	0.608	68.6	66.4	0.156
Daily intake of tea (%)	43.1	43	0.961	43.6	46.9	0.083
Daily intake of red meat (%)	8.1	6.4	0.076	11.7	8.6	<0.001
Daily intake of processed meat (%)	4.5	7	0.003	3.3	6.4	<0.001

† Information was obtained through self-report from the baseline questionnaire.
‡ *p* value on the chi-square test for categorical variables and ANOVA for continuous variables.
§ SD indicates standard deviation. BMI indicates body mass index.

CI: 0.87 - 4.88). In addition, no association between higher salted food consumption and colon cancer was seen in either males or females (HR 1.43, 95% CI: 0.66 - 3.67 and 2.21, 95% CI: 0.63 - 7.78, respectively). With regard to rectal cancer, the vegetable intake-adjusted HR in males was 3.58 (95% CI: 1.07 - 11.90). Results showed a consistently significant association between high salt intake and rectal cancer mortality in males, with a multivariate-adjusted HR of 3.94 (95% CI: 1.06 - 15.11). Further adjustment for intake of other food items, including vegetables, fruit, tea, red meat and processed meat, did not substantially alter the estimated HR. This model showed a multivariate-adjusted HR of 3.58 (95% CI: 1.08 - 11.89) for males with a high salted food intake. However, no association between high salted food intake and rectal cancer mortality was seen in females (HR 0.40, 95% CI: 0.05 - 3.47).

Table 3. Hazard ratios of digestive tract cancer deaths by salted food intake consumption according to sex

	Males (n =3074)		Females (n = 3756)	
	Low intake	High intake (95% CI)	Low intake	High intake (95% CI)
Esophagus				
Crude HR (95%CI)	1.00 (ref)	1.88 (0.47 - 7.54)	1.00 (ref)	0.93 (0.23 - 3.76)
Age-adjusted HR (95%CI)	1.00 (ref)	1.84 (0.46 - 7.38)	1.00 (ref)	0.94 (0.24 - 3.76)
Vegetables-adjusted HR (95%CI)	1.00 (ref)	1.89 (0.47 - 7.55)	1.00 (ref)	0.90 (0.23 - 3.49)
Multivariable HR† (95%CI)	1.00 (ref)	1.42 (0.30 - 6.64)	1.00 (ref)	1.18 (0.28 - 4.98)
Multivariable HR‡ (95%CI)	1.00 (ref)	1.55 (0.18 - 6.39)	1.00 (ref)	1.22 (0.35 - 5.43)
Stomach				
Crude HR (95%CI)	1.00 (ref)	2.16 (1.33 - 3.50)	1.00 (ref)	1.98 (0.82 - 4.76)
Age-adjusted HR (95%CI)	1.00 (ref)	2.24 (1.38 - 3.63)	1.00 (ref)	1.97 (0.82 - 4.74)
Vegetables-adjusted HR (95%CI)	1.00 (ref)	2.06 (1.25 - 3.39)	1.00 (ref)	1.87 (0.85 - 4.66)
Multivariable HR† (95%CI)	1.00 (ref)	2.16 (1.33 - 3.53)	1.00 (ref)	1.94 (0.81 - 4.69)
Multivariable HR‡ (95%CI)	1.00 (ref)	2.05 (1.25 - 3.38)	1.00 (ref)	1.93 (0.87 - 4.88)
Colon				
Crude HR (95%CI)	1.00 (ref)	1.14 (0.43 - 3.07)	1.00 (ref)	2.66 (0.59 - 11.9)
Age-adjusted HR (95%CI)	1.00 (ref)	1.38 (0.51 - 3.71)	1.00 (ref)	2.79 (0.62 - 12.5)
Vegetables-adjusted HR (95%CI)	1.00 (ref)	1.16 (0.35 - 2.52)	1.00 (ref)	2.13 (0.57 - 8.03)
Multivariable HR† (95%CI)	1.00 (ref)	1.36 (0.52 - 3.69)	1.00 (ref)	2.61 (0.56 - 11.9)
Multivariable HR‡ (95%CI)	1.00 (ref)	1.43 (0.66 - 3.67)	1.00 (ref)	2.21 (0.63 - 7.78)
Rectum				
Crude HR (95%CI)	1.00 (ref)	3.92 (1.03 - 14.8)	1.00 (ref)	0.40 (0.04 - 3.45)
Age-adjusted HR (95%CI)	1.00 (ref)	4.53 (1.19 - 17.2)	1.00 (ref)	0.40 (0.04 - 3.47)
Vegetables-adjusted HR (95%CI)	1.00 (ref)	3.58 (1.07 - 11.9)	1.00 (ref)	0.41 (0.05 - 3.47)
Multivariable HR† (95%CI)	1.00 (ref)	3.94 (1.06 - 15.1)	1.00 (ref)	0.41 (0.07 - 3.41)
Multivariable HR‡ (95%CI)	1.00 (ref)	3.58 (1.08 - 11.9)	1.00 (ref)	0.40 (0.05 - 3.47)

† Multivariable hazard ratio (HR) adjusted for age, body mass index, physical activity, smoking habit, alcohol habit and history of diabetes mellitus.
‡ Multivariable HR adjusted for confounding factors in HRs* and additionally adjusted for other items including vegetable, fruit, tea, red meat and processed meat intakes.
§ CI, confidence intervals.

DISCUSSION

We conducted a prospective cohort study to investigate whether a high intake of salted food increased the risk of gastrointestinal tract cancer mortality. Results showed a significant association between higher salted food consumption and stomach and rectal cancer deaths in males. These findings suggest that a high intake of salted foods influences the risk of gastrointestinal tract cancer mortality.

The dietary pattern observed in this cohort (high consumption of vegetables, fruit and tea and low consumption of red and processed meat) was similar to that reported in previous reports in Japan.[23-25] Therefore, we believe that the Miyako Study reflects a typical dietary pattern in Japan. Apart from that, some previous reports suggested that the higher consumption of vegetables may be associated with high salt intake in Japan.[21-22] Therefore, we adjusted for the possible confounding effects of vegetables, but the results showed a significant association between high salt intake and stomach and rectal cancer mortality in males.

Our current results are consistent with those of several previous population-based cohort and case-control studies.[26-29] In Japan, Tsugane *et al*.[26] reported that highest salt intake was associated with a increase in the relative risk (RR) of stomach cancer, versus the lowest salt intake as reference (RR 2.23, 95% CI: 1.48 - 3.35). In a case-control study in Japan, Hoshiyama *et al*.[27] reported that high consumption of salted food increased the risk of rectal cancer compared with low consumption of salted food (RR 1.9, 95% CI: 1.1 - 3.3). In a case-control study in Spain, Ramón *et al*.[28] reported that the risk of stomach cancer increased significantly with increasing consumption of salt (odds ratio 2.11, 95% CI: 1.21 - 7.08), while a cohort study in Finland showed that high consumption of salted fish increased the risk of colorectal cancer compared with low consumption (RR 2.58, 95% CI: 1.21 - 5.51).[29]

Several factors suggest that the link between high salted food intake and the increase in stomach and rectal cancer is N-nitroso compounds such as N-nitrosodimethylamine (NDMA). First, N-nitroso compounds are chemical compounds and potent carcinogens that can be formed from precursor compounds in foods during dry-salted processing, preservation, and preparation.[29-30] Several reports support a positive association between N-nitroso compounds and the incidence of stomach cancer.[31-34] Fur-

ther, high salt intake can damage the gastric epithelium and induce an inflammatory response, which may increase epithelial cell proliferation as part of the repair process and increase the probability of endogenous mutations.[26,33] Second, NDMA has been also shown to induce the formation of deoxyribonucleic acid adducts in human colonocytes,[29] which may initiate colorectal carcinogenesis.[35] Knekt *et al.*[29] reported an increased risk of colorectal cancer among individuals with a high intake of NDMA. Other studies have also reported an association between NDMA and an increase in colorectal cancer.[36-37] With regard to the differential association of salted food in rectal and colon cancer, one possible explanation is a difference in the cause of these cancers. Konishi *et al.*[38] suggested that cancers in the distal colon and rectum develop from preformed adenomas, a process referred to as adenoma-carcinoma sequence, whereas a *de novo* pathway was more important in lesions that arise in the proximal colon. In a previous report, N-nitroso compounds were associated with the adenoma-carcinoma-sequence with regard to the occurrence of colorectal cancer, but not with the *de novo* pathway.[39] These putative mechanisms may act together to induce stomach and rectal cancer among those with a high intake of salted food in the Japanese population.

Although the number of deaths from gastrointestinal tract cancer was relatively low, the strength of the present study was its prospective design. Information on potentially confounding variables and salted food intake was collected before the subsequent diagnosis of any cancer, reducing the potential for information bias inherent in case-control studies. In addition, there was strength in the consistency of the findings, which did not change after adjustment for other factors. Furthermore, the Miyako study is part of a large-scale population based cohort study, the Japan Collaborative Cohort Study (JACC Study) for the Evaluation of Cancer Risk, and both the Miyako and JACC study used the same food-frequency questionnaire methods to assess health-related factors.[40] Using this food-frequency questionnaire, the JACC Study has reported on a wide variety of diseases such as cancer, cardiovascular disease or diabetes mellitus,[8,23,41-43] and has contributed to public health awareness. Thus, the validity and reliability of this prospective cohort study has been reasonably assured.

Several limitations of the present study should also be mentioned. First, although salted food consumption may have changed over time, results were derived from the assessment of exposure at baseline only. Second, the type and amount of salted food consumed were not described. Third, we could not evaluate the relationship between salted food consumption and small intestinal cancer because there were only two cases in our data. Recently, however, a new endoscopic technique termed double-balloon enteroscopy that allows for complete visualization through the small intestine has been reported.[44-45] Advances in imaging techniques have therefore further facilitated the detection of small intestinal cancer, and future prospective studies may resolve the relationship between salted food consumption and this cancer.

In conclusion, this prospective cohort study showed that a high intake of salted food increased the risk of stomach and rectal cancer mortality. However, there was no association between higher salted food consumption and esophagus and colon cancer mortality. Further biochemical and epidemiological studies are required to resolve this apparent discrepancy.

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AUTHOR DISCLOSURES

All authors have no conflicts of interest to declare.

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Original Article

Prospective cohort study evaluating the relationship between salted food intake and gastrointestinal tract cancer mortality in Japan

Atsuhiko Murata MD[1], Yoshihisa Fujino PhD[1], Truong-Minh Pham PhD[1], Tatsuhiko Kubo PhD[1], Tetsuya Mizoue PhD[2], Noritaka Tokui PhD[3], Shinya Matsuda PhD[1], Takesumi Yoshimura PhD[4]

[1]*Department of Preventive Medicine and Community Health, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan*
[2]*Department of Epidemiology, Research Institute, International Medical Center of Japan, Tokyo, Japan*
[3]*Department of Preventive Medicine and Dietetics, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan*
[4]*Fukuoka Institute of Health and Environmental Sciences, Fukuoka, Japan*

探討日本塩漬食物攝取與胃腸道癌死亡率關係之前瞻性世代研究

目的：探討高塩食物的摄入是否增加胃肠道癌症死亡的風险。方法：以一项前瞻性研究评估 6,830 位日本居民塩漬食品消费和消化道癌症死亡率风险的关系。數据取自日本一前瞻性世代研究。從基线問卷调查的結果，依塩漬食品的消费量，歸類為低摄入量與高摄入量两組。使用 Cox 比例风险模型来估计风险比(HR)和 95%信赖区间。结果：共計 94,996 人年的随访中，消化道癌死亡有 174 例(47 例食道癌、胃癌 87 例、23 例结肠癌和直肠癌 17 例)，平均随访 8.9 年。經過年齡，身体质量指数，体能活动，吸烟，饮酒，糖尿病史和饮食项目，包括蔬菜、水果、茶叶、红肉和加工肉的校正後，高塩摄入量在男性胃癌的风险比為 2.05 (95%信赖区间：1.25 - 3.38)，對直肠癌为 3.58 (95%信赖区间：1.08 - 11.89)。反之在女性卻没有关联。此外，不论男女性，高塩食品消费和食道癌或结肠癌之间都没有相关。结论：較高的塩漬食品消费和男性胃癌及直肠癌的死亡率有显着相关，但在女性則無。而高塩食品消费與男性或女性的食道癌或结肠癌死亡率没有关联。

關鍵字：前瞻性世代研究、胃肠道癌症、飲食、死亡率、塩漬食品