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Reported amount of salt added to food is associated with increased all-cause and cancer-related mortality in older men in a prospective cohort study.

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Abstract

Background: The effect of dietary salt intake on important population outcomes such as mortality is controversial. The aim of this study was to examine the association between the dietary habit of adding salt to food and mortality in older men.

Design, participants, setting and measurements: A risk factor questionnaire which contained a question about the dietary habit of adding salt to food was completed by 11742 community recruited older men between 1996 and 1999. The men were followed by means of the Western Australia Data Linkage System until November 30th 2010. Deaths due to cardiovascular diseases and cancers were identified using ICD-10 codes in the ranges I00-I99 and C00-D48, respectively. The association between the frequencies of adding salt to food and mortality was assessed using Kaplan Meier estimates and Cox proportional hazard analysis.

Results: Median follow-up for survivors was 13.1 years (range 11.8-14.6 years). A total of 5399 deaths occurred of which the primary cause registered was cancer and cardiovascular disease in 1962 (36.3%) and 1835 (34.0%) men, respectively. The reported frequency of adding salt to food was strongly positively associated with all-cause (p<0.001), cancer-related (p<0.001) but not cardiovascular-related (p=0.649) mortality. Men reporting adding salt to their food always had a 1.12-fold (95% CI 1.05-1.20, p<0.001) and a 1.20-fold (95% CI 1.07-1.34, p=0.001) increased risk of all-cause and cancer-related mortality, respectively, after adjusting for other risk factors. Men reporting adding salt to their food sometimes had a 1.17-fold (95% CI 1.05-1.30, p=0.004) increased risk of cancer-related mortality after adjusting for other risk factors.

Conclusion: A history of adding salt to food is associated with increased cancer-related mortality in older men.

Key words: Salt; mortality; men.

Introduction

Good evidence suggests that high salt intake is associated with hypertension and current clinical guidelines and public health policies recommend low salt intake [1-4]. Despite these recommendations the evidence that reducing dietary salt intake decreases mortality is limited and sodium is accepted to be an essential extracellular cation required to maintain hydroelectric balance [5-13]. Findings from a number of studies have associated low salt intake with increased mortality [5-11]. High salt intake has also associated with increased mortality [12, 13]. The previous studies have not been focused on community recruited older men or assessed reported salt added to food which is an aspect easier to assess in community samples. The aim of the current study was to examine the association of the dietary habit of adding salt to food with mortality in a large cohort of older men recruited as part of a community screening study.

Methods

Study population: The Health in Men Study (HIMS) developed from a population-based randomized trial of screening for abdominal aortic aneurysm (AAA) conducted in Perth, Western Australia between 1996 and 1999 which has been previously described in detail [14, 15]. Ethics approval for the study was provided by The University of Western Australia Ethics Committee (Project numbers RA/4/1/5765) and all men provided written informed consent.

Assessment of recruited men: Each man was invited to complete a questionnaire assessing aspects of history and lifestyle relevant to AAA and cardiovascular disease including: smoking history; history of diagnosis of high blood pressure, angina, myocardial infarction, stroke, diabetes and high cholesterol; history of treatment for high blood pressure, angina, diabetes and high cholesterol; frequency of eating meat (≥6 times/week, 3–5/week, 1–2/week, <1/week or never); frequency of eating fish (≥6 times/week, 3–5/week, 1–2/week, <1/week or never); and hours of non-vigorous exercise (none, ≤2 hours/ week, >2-4 hours/ week, >4-6 hours/ week or >6 hours/ week). Salt addition to food was assessed with the following question 'Do you add salt to your food?' with three possible answers: (a) rarely or never, (b) sometimes, (c) almost always or always. Waist and hip circumference were measured in accordance with guidelines of the International Society for the Advancement of Kinanthropometry [16] . Body mass index was calculated as weight in kilograms divided by height in meters squared as previously described [16]. The greatest transverse and antero-posterior diameter of the infra-renal aorta was measured using a Toshiba Capasee ultrasound machine with a 3.75 MHz probe (Toshiba Australia, North Ryde, NSW). Assessment of intraobserver and interobserver reproducibility in aortic diameter measurement was carried out every 4 months on 10 randomly selected subjects, as previously reported [17]. No significant differences were found between observers with 95% of measurement differences being <3 mm [17]. An AAA was defined by infra-renal aortic diameter ≥30mm.

Follow-up and outcome assessment: All men were followed from the time of recruitment until 30th November 2010 by means of the Western Australia Data Linkage System. Deaths due to cardiovascular diseases and cancers were identified from the Death Registry using ICD-10 codes in the ranges I00-I99 and C00-D48, respectively, as previously described [18]. The validity of data within the Western Australia linked Death Registry has been previously assessed and found to be good [14].

Statistical analyses: All analyses were performed using IBM SSPS Statistics version 22 (St. Leonards, New South Wales, Australia), and the publically available R software package.

The association of reported salt added to food with all-cause, cancer-related and cardiovascular-related mortality was assessed using Kaplan Meier estimates and Cox proportional hazard analysis. For these analyses men that were still alive were censored at the time of the data linkage. For the cause specific death analyses all men were included and men who died of causes unrelated to the outcome of interest were censored at the date of their death. Initially univariate Cox proportional hazard analysis was performed to assess the association of individual risk factors with: i) all-cause, ii) or cancer-related mortality. Subsequently the association of reported salt added to food with all-cause mortality was adjusted for age (per 5 years), past treatment for hypertension, past treatment for angina, past history of myocardial infarction, past history of stroke, past treatment for diabetes, ever smoking, waist to hip ratio), frequency of eating fish, frequency of non-vigorous exercise and AAA presence, based on significant associations of the risk with all-cause mortality following univariate Cox regression. Similarly, the association of reported salt added to food with cancer-related mortality was adjusted for age (per 5 years), past treatment for dyslipidaemia, ever smoking, waist to hip ratio, body mass index, frequency of eating meat, frequency of non-vigorous exercise and AAA presence. The proportional hazards assumption was assessed for models predicting all-cause or cancer-relating mortality. In order to fulfil the proportional hazards assumption during multivariate analyses, participants were re-categorised into groups with waist to hip ratios of 0.9-1.02, and >1.02. Similarly, participants were re-categorised into groups with BMI of 20-30, 30-49 and >40.

Cumulative mortality was compared between men who reported adding salt to their food never, sometimes or always using log rank test.

Results

Characteristics of the included men

Risk factors for the 11742 men reporting the frequencies of adding salt to food at the time of recruitment have been previously published [19] [20].

Median follow-up for survivors was 13.1 years (range 11.8-14.6 years). A total of 5399 deaths occurred during follow-up of which the primary cause registered was cancer and cardiovascular disease in 1962 (36.3%) and 1835 (34.0%) men, respectively. The types of cancer registered as the primary cause of death included those of respiratory tract (n=503), gastro-intestinal tract (n=473), urogenital (n=373), hematological (n=237) and miscellaneous (including skin, soft tissue, muscle, skeletal, brain, thyroid, multiple sites and unknown site; n=376) origins. The all-cause mortality rates were 13.2, 32.3 and 45.1% at 5, 10 and 13 years, respectively. The cancer-related mortality rates were 5.7, 13.9 and 19.3% at 5, 10 and 13 years, respectively. The cardiovascular disease-related mortality rates were 5.0, 12.5 and 18.3% at 5, 10 and 13 years, respectively.

Association of reported frequencies of adding salt to food with mortality

Figures 1-3 illustrate the relationship between reported frequencies of adding salt to food and subsequent all-cause, cancer-related and cardiovascular-related mortalities. Reported frequencies of adding salt to food was strongly positively associated with all-cause (Figure 1; $p<0.001$), cancer-related (Figure 2; $p<0.001$) but not cardiovascular-related (Figure 3; $p=0.649$) mortality. Men reporting the addition of salt to food never, sometimes or always had a cumulative incidence of all-cause mortality of 43.3, 45.0 and 47.6% at 13 years, respectively. Men reporting the addition of salt to food never, sometimes or always had a cumulative incidence of cancer-related mortality of 16.9, 20.2 and 21.3% at 13 years, respectively. Men reporting the addition of salt to food never, sometimes or always had a cumulative incidence of cardiovascular disease-related mortality of 18.5, 18.1 and 18.1% at 13 years, respectively.

Creating multivariate models to predict all-cause and cancer-related mortality

In order to further assess the association of reported frequencies of adding salt to food with mortality univariate Cox proportional hazard ratios were calculated to assess the association of baseline risk factors with all-cause and cancer-related mortality (Table 1). Risk factors showing significant associations with each outcome via univariate regression were included as covariates in multivariable Cox proportional hazards models to assess the impact of salt consumption on all-cause and cancer-related mortality as appropriate. Ten men with incomplete risk factor data were excluded from multivariate analysis (n for multivariable analyses = 11732).

Diagnostic statistics demonstrated that the multivariable Cox regression model assessing the relationship of salt consumption with all-cause mortality did not conform with the proportional hazards assumption. To correct this, several variables (previous history of diabetes, ever smoking and frequency of non-vigorous exercise) were stratified prior to entering the model (Table 2). After adjusting for potential confounders, men who reported that they always added salt to their foods had a 1.12-fold (95% CI 1.05-1.20 $p<0.001$) increased risk of all-cause mortality compared to those who never added salt to their food (Table 2). No significant difference in all-cause mortality was noted for men who sometimes added salt to their food.

The model assessing the association of salt consumption with cancer-related mortality conformed to the proportional hazards assumption, thus, no further data manipulations were performed. Men who reported sometimes or always adding salt to their food had significantly increased risk of cancer-related mortality (hazards ratio: 1.16 (95% CI 1.04-1.29), and 1.20 (95% CI 1.07-1.34) respectively), compared to those who never added salt (Table 3).

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Discussion

The current study examined the incidence of mortality in a group of community recruited older men over a long follow-up of approximately 13 years. Approximately 70% of deaths were secondary to cardiovascular and cancer-related causes in keeping with the accepted main causes of mortality in Western communities. The main finding from this study was that always adding salt to food was associated with increased all-cause and cancer-related mortality in older men. The reliability of this association is supported by the large number of men examined (11742), the long follow-up and the adjustment for potential confounding risk factors. Furthermore the validity of the data is supported by the expected associated of age, cardiovascular risk factors and past history of cardiovascular disease with mortality.

Randomized controlled trials suggest that limiting salt intake can reduce resting systolic blood pressure by approximately 3-4 mmHg during short term follow-up [2, 21]. Randomized trials have however failed to demonstrate convincingly that limiting dietary salt intake reduces cardiovascular events or mortality possibly because these studies have been under powered [22]. Restricting sodium intake has also been associated with some detrimental effects in experimental studies such as activation of the renin-angiotensin system [23, 24]. Thus the value of dietary salt restriction in improving health is currently controversial [1, 25].

A number of prospective studies have examined the association of measures of dietary salt intake, such as dietary questionnaires or 24 hour sodium excretion with mortality with conflicting results [5-13, 26-30].. Three community based studies have associated high salt intake with increased cardiovascular disease or stroke-related mortality in Japan and Europe [12, 14, 26]. In contrast community based studies in the USA and Europe have associated low salt intake with increased mortality [5, 9, 11]. Furthermore studies in patients with diabetes and renal failure have also associated low salt intake with increased mortality [7, 8, 10]. Some studies have suggested that the association between salt intake and cardiovascular death is J-shaped with subjects with low and high sodium excretion having increased mortality[6] . The current study is one of the largest studies to assess the association of adding salt to food with mortality and of note included follow-up for over ten years. While adding salt to food was assessed by a simple question this approach was a very practical way of assessing a large population of older men. It is also possibly a more practical way of advising patients on dietary behavior in that we looked at the specific practice of adding salt to food rather than measures of total salt intake. Data using this approach is also relevant to advising older subjects who may find it very difficult to gauge accurate estimates of sodium intake. Overall we found no association between reported frequency of adding salt to food and cardiovascular mortality.

There are a number of possible reasons for this finding. It is possible that high dietary salt intake while predisposing to higher blood pressure in the short term may stimulate other mechanisms in the longer term which correct blood pressure. In support of this theory we previously found no association between reported frequencies of adding salt to food and resting blood pressure [20][19]. Most of the trials examining the effect of modifying salt intake on blood pressure have follow-up limited to weeks [2, 21]. It is also possible that a single assessment of the frequency of adding salt to food may not be reflective of dietary behavior over a prolonged follow-up period, and that change in salt consumption during the period of follow-up might not have been captured. These considerations may have complicated our assessment of the association of reported frequencies of adding salt to food with mortality although we adjusted our analyses for cardiovascular risk factors and past history of cardiovascular disease.

The association between dietary salt intake and cancer-related mortality has been relatively little studied [27-30]. High dietary salt intake has been positively associated with mortality from stomach cancer in Japanese, Chinese and European populations [26-29]. In the current study men reporting adding salt to their food always had a 1.22-fold increased incidence of cancer-related mortality. This association remained after adjusting for other risk factors that we examined. This finding is in line with experimental and epidemiology data suggesting the role of salt in promoting some cancers such as those within the gastro-intestinal tract [31, 32]. As expected in a cohort of older men the reported cancer types in this series included not only gastro-intestinal but also respiratory, urogenital, hematological and those from other sites. Thus it is possible that the behavior of adding salt always to food may promote cancers at sites other than the gastro-intestinal tract although this requires more specific assessment.

A number of possible limitations of this study should be considered including measurement error, reverse causality and residual confounding. Firstly, our assessment of salt added to food was limited to a simple but practical question in which we asked whether salt was added to food never or rarely, sometimes, almost always or always. More sophisticated assessment methods, such as measured of 24-hour urinary sodium excretion, were not used. This approach may have introduced measurement error. It is however accepted that even biochemical methods of estimating salt intake are open to measurement error and self-reported dietary intake of salt has been found to be reflective of 24 hour urinary sodium excretion, suggesting that self-report is a valid measure of salt intake[33]. Secondly, we only examined salt added to food on one occasion rather than repeated assessments which would have been ideal. Thirdly, this study is a prospective longitudinal human association study. It is not possible to definitively conclude that the association between always adding salt to food and mortality is causative. The direct role of salt in mortality could only be established by a randomized controlled trial of at risk individuals in which the effect of administering different amounts of salt was compared. Based on data from the current study such a trial would require a large number of subjects and extended follow-up in order to assess the efficacy of salt restriction in limiting mortality. Fourthly, we may have failed to adjust for some confounding factors. The current study included a large number of men and used adjustment for recognized confounding factors such as age, hypertension, high cholesterol, coronary heart disease and stroke. It is possible that other confounding factors which we were not able to assess, such as fruit and vegetable intake, may have contributed to our finding.

In conclusion the current study suggests that the addition of salt to food always is associated with increased mortality in older men through the promotion of cancer-related deaths. This information supports the concept that dietary salt addition to food should be limited.

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Author roles:

Study design: JG; Data collection: GJH, BBY, LF, PEN; Data analysis: JG, JVM, REJ KM; Data interpretation: All authors; drafting of manuscript: JG; Critical revision of manuscript: All authors.

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Figure Legends

Figure 1: Kaplan Meier curves showing the cumulative mortality from all causes in relation to reported frequencies of adding salt to food. Lines represent cumulative mortality for subjects grouped by reported frequencies of adding salt to food. The blue line represents men reporting the addition of salt to food never; the green line represents men reporting the addition of salt to food sometimes; and the brown line represents men reporting the addition of salt to food always. Vertical lines represent subjects censored at loss to follow-up.

Figure 2: Kaplan Meier curves showing the cumulative mortality from cancer in relation to reported frequencies of adding salt to food. Lines represent cumulative mortality for subjects grouped by reported frequencies of adding salt to food. The blue line represents men reporting the addition of salt to food never; the green line represents men reporting the addition of salt to food sometimes; and the brown line represents men reporting the addition of salt to food always. Vertical lines represent subjects censored at loss to follow-up.

Figure 3: Kaplan Meier curves showing the cumulative mortality from cardiovascular diseases in relation to reported frequencies of adding salt to food. Lines represent cumulative mortality for subjects grouped by reported frequencies of adding salt to food. The blue line represents men reporting the addition of salt to food never; the green line represents men reporting the addition of salt to food sometimes; and the brown line represents men reporting the addition of salt to food always. Vertical lines represent subjects censored at loss to follow-up.

Table 1: Univariate association of risk factors with all-cause mortality in 11,742 older men.

Characteristic	**Number**	**All-cause**			**Cancer-related**		
		Hazard ratio	**95% CI**	**P value**	**Hazard ratio**	**95% CI**	**P value**
Reported salt addition to food:							
Rare	4466	1.00	Reference		1.00	Reference	
Sometimes	3787	1.06	0.99-1.13	0.078	1.24	1.11-1.38	<0.001
Always	3489	1.16	1.08-1.23	<0.001	1.32	1.18-1.47	<0.001
Age per 5 years*	11742	1.81	1.76-1.87	<0.001	1.48	1.41-1.56	<0.001
Past treatment for hypertension	4202	1.30	1.24-1.38	<0.001	1.05	0.95-1.15	0.343
Past treatment for angina	1120	1.62	1.50-1.76	<0.001	1.08	0.93-1.26	0.325
Past history of myocardial infarction	1711	1.70	1.59-1.81	<0.001	1.07	0.94-1.22	0.338

Past history of stroke	903	1.86	1.71-2.02	<0.001	1.17	0.99-1.39	0.064
Past treatment for diabetes	1333	1.45	1.34-1.56	<0.001	1.11	0.96-1.28	0.146
Treatment for high cholesterol	2264	1.01	0.95-1.08	0.733	0.83	0.74-0.94	0.002
Ever smoker	8337	1.43	1.35-1.53	<0.001	1.56	1.41-1.74	<0.001
WHR per 0.06*	11736	1.07	1.04-1.09	<0.001	1.05	1.00-1.09	0.046
BMI per 4 kg/m^2*	11733	0.92	0.89-0.95	<0.001	0.94	0.90-0.99	0.018
Eat meat (times per week)							
≥6	3387	1.00	0.81-1.23	0.998	1.53	1.01-2.32	0.046
3-5	5316	0.94	0.77-1.16	0.557	1.40	0.92-2.11	0.115
1-2	2339	0.92	0.74-1.13	0.413	1.39	0.92-2.12	0.123
<1	503	0.92	0.73-1.18	0.520	1.09	0.68	1.76
Never	197	1.00	Reference		1.00	Reference	
Eat Fish (times per week)							
≥6	113	0.75	0.55-1.04	0.085	0.72	0.41-1.27	0.255

3-5	1141	0.77	0.63-0.93	0.006	0.87	0.63-1.20	0.394
1-2	7337	0.78	0.65-0.92	0.004	0.84	0.62-1.14	0.257
<1	2908	0.76	0.63-0.91	0.002	0.88	0.65-1.20	0.423
Never	243	1.00	Reference		1.00	Reference	
Non-vigorous exercise (hours per week)							
None	4122	1.00	Reference		1.00	Reference	
≤2	1641	0.93	0.85-1.01	0.075	0.97	0.84-1.11	0.658
>2-4	2221	0.87	0.81-0.94	<0.001	0.92	0.81-1.04	0.190
>4-6	1209	0.79	0.72-0.87	<0.001	0.82	0.70-0.97	0.019
>6	2549	0.88	0.82-0.95	0.001	0.93	0.83-1.05	0.260
AAA	931	1.76	1.62-1.92	<0.001	1.47	1.27-1.71	<0.001

Men with the risk factor were compared to subjects without the risk factor or those with the reference reported level of intake or activity. *Approximate standard deviation. WHR= Waist to hip ratio; BMI= Body mass index; AAA= Abdominal aortic aneurysm. WHR was missing on 6 men. BMI was missing on 9 men.

Table 2: Multivariate model examining the association of reported frequency of adding salt to food and all-cause mortality in 11,732 older men.

Characteristic	Number	Hazard ratio	95% CI	P value
Reported salt addition to food:				
Rare	4462	1.00	Reference	
Sometimes	3784	1.02	0.96-1.09	0.489
Always	3486	1.12	1.05 – 1.2	<0.001
Age per 5 years*	11732	1.76	1.71-1.82	<0.001
Past treatment for hypertension	4198	1.13	1.07-1.20	<0.001
Past treatment for angina	1120	1.18	1.09-1.29	<0.001
Past history of myocardial infarction	1710	1.37	1.28-1.48	<0.001
Past history of stroke	902	1.45	1.32-1.58	<0.001
WHR <0.9	1854	1.00	Reference	
WHR 0.9-1.02	8110	1.03	0.95-1.11	0.507
WHR >1.02	1768	1.20	1.08-1.33	0.001
Eat Fish (times per week)				
≥6	112	0.67	0.49-0.93	0.017
3-5	1141	0.81	0.67-0.98	0.031

1-2	7330	0.83	0.69-0.98	0.032
<1	2907	0.85	0.71-1.01	0.066
Never	242	1.00	Reference	
AAA	872	1.37	1.25-1.49	<0.001

Men with the risk factor were compared to subjects without the risk factor or those with the reference reported level of intake or activity. All variables shown were included in the multivariate model. Reported levels of non-vigorous exercise, prior treatment for diabetes or ever smoking were included in the model as stratified variables, therefore hazards ratios cannot be calculated.

*Approximate standard deviation. WHR= Waist to hip ratio; AAA= Abdominal aortic aneurysm.

Table 3: Multivariate model examining the association of reported frequency of adding salt to food and cancer-related mortality in 11,732 older men.

Characteristic	Number	Relative risk	95% CI	P value
Reported salt addition to food:				
Rare	4462	1.00	Reference	
Sometimes	3784	1.16	1.04-1.29	0.007
Always	3486	1.20	1.07-1.34	0.001
Age per 5 years*	11732	1.46	1.39-1.54	<0.001
Past treatment for dyslipidaemia	2264	0.84	0.74-0.94	0.004
Ever smoker	8328	1.48	1.33-1.65	<0.001
BMI<20	276	1.00	Reference	
BMI 20-30	9334	0.59	0.45-0.78	<0.001
BMI 30-39	2093	0.51	0.38-0.69	<0.001
BMI >40	29	0.91	0.39-2.14	0.833
Eat Meat (times per week)				
≥6	3382	0.70	0.46-1.07	0.099
3-5	5314	0.78	0.60-1.00	0.052
1-2	2336	0.96	0.85-1.10	0.568
<1	503	0.95	0.86-1.06	0.343
Never	197	1.00	Reference	

Non-vigorous exercise (hours per week)				
None	4116	1.00	Reference	
≤2	1640	0.99	0.86-1.14	0.856
>2-4	2221	0.93	0.82-1.06	0.283
>4-6	1209	0.84	0.72-0.99	0.039
>6	2546	0.94	0.83-1.06	0.314
AAA	872	1.26	1.08-1.47	0.004

Men with the risk factor were compared to subjects without the risk factor or those with the reference reported level of intake or activity. All variables shown were included in the multivariate model. *Approximate standard deviation. WHR= Waist to hip ratio; AAA= Abdominal aortic aneurysm.

Figure 1

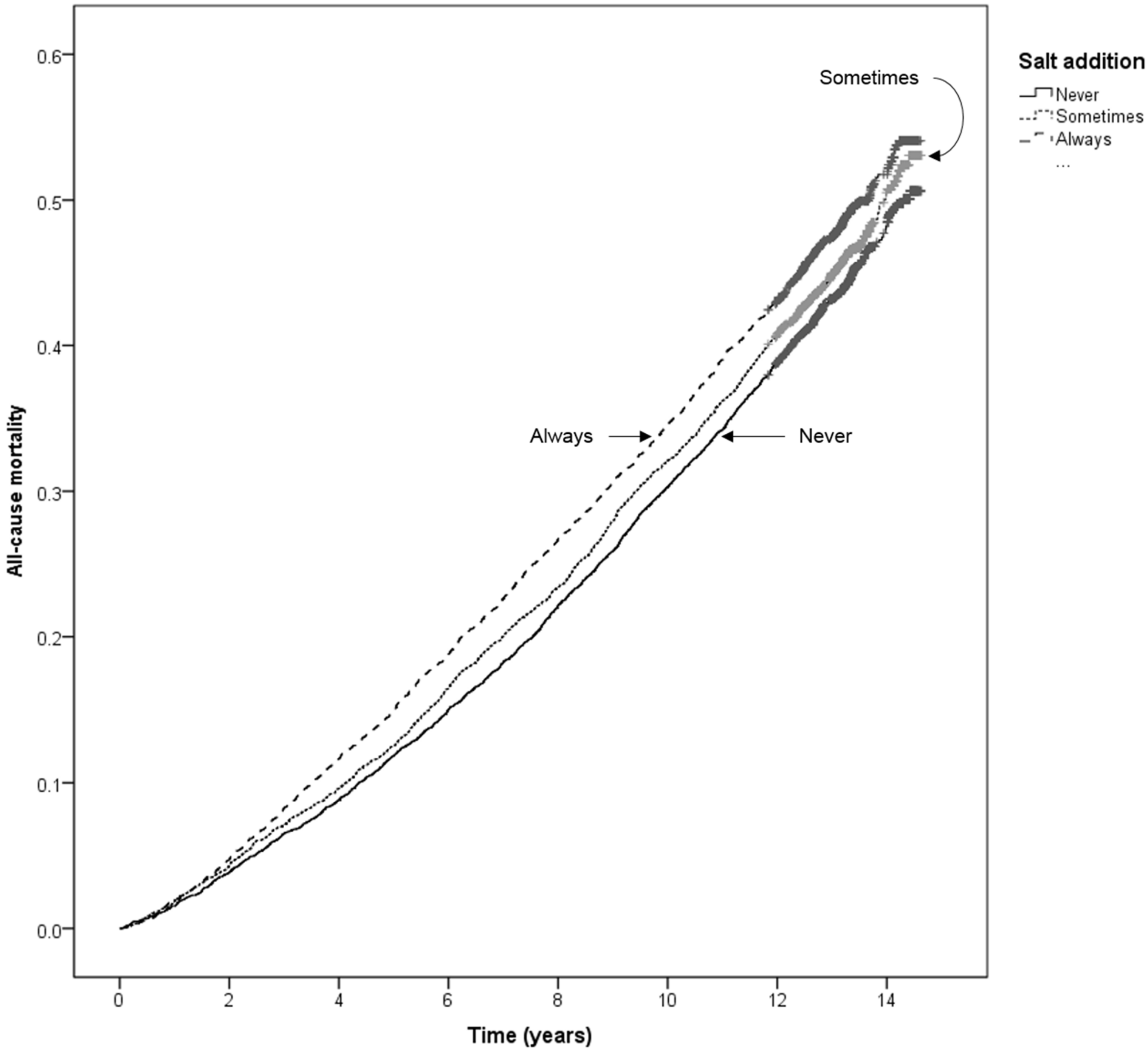
0.6
0.5
0.4
0.3
0.2
0.1
0.0
All-cause mortality
0
2
4
6
8
10
12
14
Time (years)
Sometimes
Always
Never
Salt addition
Never
Sometimes
Always

Figure 2

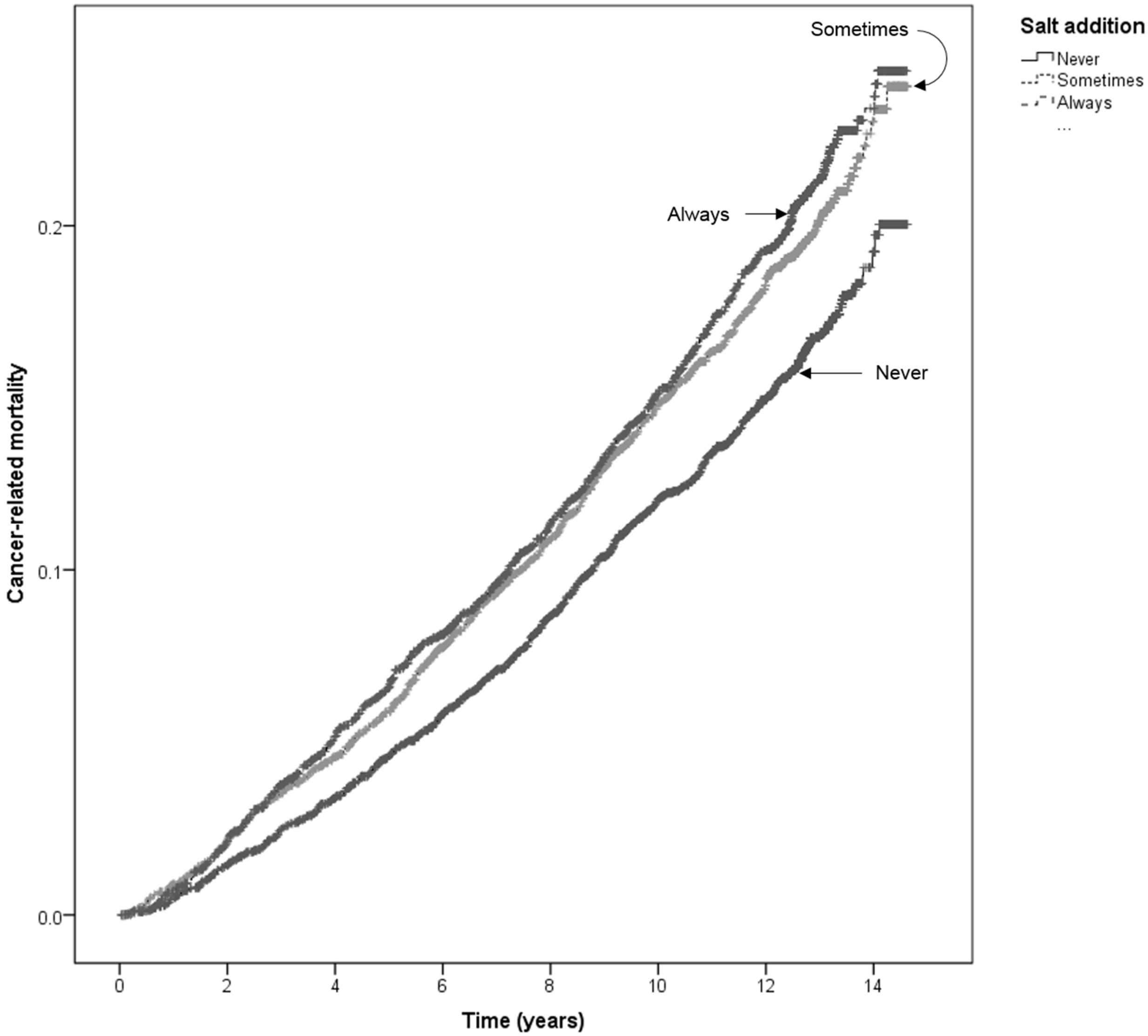
Sometimes
Always
Never
Salt addition
Never
Sometimes
Always
0.2
0.1
0.0
Cancer-related mortality
0
2
4
6
8
10
12
14
Time (years)

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Figure 3