Adding salt to food as an indicator of gastric cancer risk among adults: A prospective study

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Abstract

Background: While dietary salt intake has been linked with gastric cancer risk in Asian studies, findings from Western populations are sparse and limited to case-control studies.

Methods: We evaluated associations between the frequency of adding salt to food and the risk of gastric cancer in a large prospective cohort of UK adults, the UK Biobank (N=471,144). Frequency of adding salt to food was obtained from a touchscreen questionnaire completed by participants at baseline (2006-2010). 24-h urinary sodium excretion was estimated using INTERSALT formulae. Cancer incidence was obtained by linkage to national cancer registries.

Results: During the median 10.9 years of follow-up, 640 gastric cancer cases were recorded. In multivariable models, participants reporting adding salt to food “always” had a 41% higher risk of gastric cancer compared to participants who reported adding salt to food “never/rarely” (95%CI: +4%, +91%). There was a positive graded association between the frequency of adding salt to food and estimated 24-h urinary sodium. On the other hand, associations of estimated 24-h urinary sodium with gastric cancer were nonsignificant.

Conclusions: “Always adding salt to food” was associated with a higher gastric cancer risk in a large sample of UK adults participating in the UK Biobank study compared to “never/rarely” adding salt to food. Frequency of adding salt to food can serve as a useful indicator of salt intake for surveillance purposes and a basis for devising easy-to-understand public health messages.

Mini-abstract

High frequency of adding salt to food was associated with a higher risk of gastric cancer among UK adults independent of age, sex, ethnicity, tobacco and alcohol use, prevalent morbidity, diet, or BMI. This is the first prospective study to show that frequently adding salt to food is related to higher gastric cancer risk in a western population. “Always adding salt to food” can serve as a simple indicator of excessive sodium intake for surveillance purposes and a basis for formulating public health messages aimed at gastric cancer prevention.

Introduction

Gastric cancer is the fifth most prevalent cancer globally [1], with the highest prevalence in Asia, followed by Eastern Europe and Latin Americas [2]. Male sex and older age are established risk factors of gastric cancer, while other factors include tobacco and alcohol use, H. pylori infection, consumption of some Asian-style salt-preserved foods, and being overweight/obese [3–6]. After initial successes in reducing gastric cancer rates in the second half of the past century, recent studies are raising concerns as they are now increasing among young adults (< 50 years) globally [7–10].

The role of dietary salt intake in gastric cancer risk has been widely investigated, yet the evidence is inconclusive [1, 11]. Some studies hypothesize its role in disrupting stomach mucosa and making it more susceptible to *H. Pylori* colonization [3, 12]. Salt may also increase gastric cancer risk via mechanisms independent of *H. Pylori* infection, for example by damaging the gastric epithelium in synergy with N-nitroso compounds and chemical carcinogens [13]. While there is strong evidence on the role of consumption of some salt-preserved foods in gastric cancer aetiology, data on intakes of added or total salt yielded mixed results, with the majority of studies conducted in Asian populations with higher gastric cancer prevalence [1]. This may partly be attributed to methodological issues in measuring dietary salt intake [14]; repeated 24-h urinary sodium excretion, the “gold standard” method for estimating sodium intake is expensive and burdensome, making it impractical for use in large samples required for evaluating associations with rare outcomes; using spot urine samples to estimate salt exposure, on the other hand, is prone to random error due to variation in sodium intake and hence urinary sodium excretion. While a number of formulae for estimating 24-h urinary sodium from spot urine exist, they have been criticized for differential misclassification (e.g. overestimating intake in some and underestimating in other population groups)[14–16]. Finally, it is difficult to accurately estimate sodium intake with self-report diet assessment instruments such as 24-h diet recalls (24-h recalls) or food frequency questionnaires (FFQs) due to highly variable sodium content in packaged products and respondent difficulty in guessing the amount of salt added during cooking or at the table [17, 18].

Self-reported data on “adding salt to food” are a simple measure of habitual salt intake not influenced by day-to-day variation in intakes and may be converted to an easy-to-understand-and-apply public health message. In a recent study of UK Biobank participants, high frequency of adding salt to food was associated with higher spot urine sodium concentrations and with a higher risk of premature mortality [19]. As only a few prospective studies have evaluated associations between salt intake with gastric cancer [11], with the majority of findings coming from Asian populations, we investigated the association between habitual adding salt to food and the risk of stomach cancer in a large prospective sample of UK adults.

Methods

Study population

We used data from the UK Biobank, a large population-based prospective study of UK adults that has been described in detail elsewhere [20]. In our study, data of 502,367 participants were available for analysis. 27,085 study participants with prevalent cancer at baseline (any cancer except for non-melanoma skin cancer), and 3,308 participants reporting having existing kidney disease (self-reported during verbal interview) (Supplemental Fig. 1). We also excluded 1,082 participants for whom data on adding salt to food was missing (either missing at baseline or ‘prefer not to answer’) and 18,877 participants with missing data on urinary sodium levels. Thus, our analyses of associations between adding salt to food and gastric cancer included 471,144 participants, while those with urinary sodium were restricted to 453,349 participants.

Exposure, covariate and outcome assessment

The exposure was ascertained using a variable on adding salt to food measured by the baseline touch-screen questionnaire (2006–2010, Data-Field 1478). Participants were asked: “Do you add salt to your food? (Do not include salt used in cooking)” and could choose one of the following answers: “never/rarely”, “sometimes”, “usually”, “always” and “prefer not to answer”. Urinary sodium, creatinine and potassium were measured at baseline from random spot urine samples by the Ion Selective Electrode method using Beckman Coulter AU5400, UK Ltd [21]. We estimated 24-h urinary sodium using INTERSALT equations for men and women [22, 23].

Sociodemographic (sex, age, ethnicity, education level, Townsend deprivation index) and lifestyle (diet, smoking, alcohol use, physical activity) covariate data were obtained from the baseline touch-screen questionnaire. Body mass index (BMI) was calculated from weight and height measured by trained staff at recruitment; use of diuretics was reported by participants during verbal interview at baseline. Multimorbidity was estimated using a previously described approach [24] [25]. *H. pylori* infection status was obtained from verbal interview at baseline (self-reported) and hospital impatient data.

Finally, gastric cancer status was ascertained by linkage to the national cancer registries (ICD-10, C16). Cancer diagnosis data were provided through record linkage to National Cancer Registries in England, Wales (follow-up data available from the NHS Information Centre until February 2020), and Scotland (follow-up data available from the NHS Central Register of Scotland until January 2021).

Statistical analysis

In statistical analysis, we used general linear models to evaluate the associations between frequency of adding salt to food with spot urinary sodium and estimated 24-h urinary sodium concentrations. Associations between the frequency of adding salt to food and gastric cancer risk were assessed using proportional Cox hazards models with age as the time scale. Age at baseline was defined as age at entry, and age at diagnosis, death, or latest follow-up (whichever occurred first) was used as age at exit. Models were first adjusted for sex and ethnicity (white, black, Asian, other), with multivariable-adjusted models further including education level (low, medium, high, missing), Townsend deprivation index (in quintiles), smoking status (never, previous, current, missing (19%)), body mass index (continuous), physical activity level (MET hours/week), alcohol consumption (< 1g/d, 1-7g/d, 8–15 g/d, ≥ 16g/d, missing (24%)), use of diuretics (yes/no), and multimorbidity (number of prevalent long-term conditions: 0, 1, 2, > 2). Finally, models were adjusted for dietary factors obtained at baseline (beef intake, pork intake, processed meat intake, fresh fruit intake, salad/raw vegetable intake, and cooked vegetable intake). For use in models, we summed up beef, pork and processed meat intake as “red meat intake” and fruit and vegetable intakes into “fruit and vegetable intake” and categorized these scores into tertiles. Cox regression models with urinary sodium as the exposure (tertiles) based on the INTERSALT formulae were carried using the similar multivariable models as for added salt, albeit without adjustment for BMI, as it was already included in the formulae. In sensitivity analyses, we excluded gastric cancer cases occurring in the first year of follow-up (N = 38), participants with multimorbidity (2 or more long-term conditions) and participants with

a positive *H. pylori* infection status. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc). All statistical tests were two sided, and P = 0.05 was considered to be statistically significant.

Results

Characteristics of the study population

The final analysis included 471,144 participants. Over the period of median 10.9 years of follow-up, 640 gastric cancer cases were recorded. Participants (Table 1) reporting “always” adding salt to food were more likely to be male, non-white, to have a lower education level and a higher Townsend deprivation index; they were more likely to be a past/current smoker, to have alcohol high alcohol intakes.

Added salt and gastric cancer risk

Table 2 shows the main findings of our study. In sex and ethnicity-adjusted models, hazard ratio between participants who reported “always” adding salt to food and participants who reported adding salt to food “never/rarely” (reference group) was HR = 1.88 (95% CI: 1.41, 2.52); in multivariable models this hazard was HR = 1.39 (95% CI: 1.02, 1.88). The results did not considerably change after adjusting for dietary factors; hazard ratio was HR = 1.41 (95% CI: 1.04, 1.91). In sensitivity analyses, hazard ratios in models adjusted for dietary factors were: HR = 1.45 (85%CI: 1.06, 1.98) after excluding cases in the first year of follow-up; HR = 1.32 (95% CI: 0.88, 1.99) after excluding multimorbidity cases; and HR = 1.39 (95% CI: 1.02, 1.89) after excluding persons with *H. pylori* infection at baseline.

Urinary sodium and gastric cancer risk

Figure 1 shows a graded positive association between the spot urinary sodium and estimated 24h urinary sodium with the frequency of adding salt to food to food. Hazard ratios between the top tertile and the reference tertile of estimated 24h urinary sodium and gastric cancer in age and ethnicity-adjusted models were HR = 1.40 (95% CI: 1.03, 1.90) (Table 3). In multivariable-adjusted models the hazard ratio was HR = 1.27 (95% CI: 0.93, 1.74). After excluding gastric cancer cases occurring in the first year of follow-up hazard ratio was HR = 1.39 (95%CI: 1.01, 1.93, p-trend = 0.01). The results did not considerably change with exclusion of *H. pylori* cases, and were somewhat weaker when multimorbidity cases were excluded.

Discussion

In this prospective study of UK Biobank participants, we found a positive association between always adding salt to food and the risk of gastric cancer independent of demographic, socioeconomic and lifestyle factors and irrespective of prevalent comorbidities. We also found that adding salt to food had a graded positive association with spot urinary sodium and 24h urinary sodium excretion estimated by INTERSALT formulae. In multivariable-adjusted models, nevertheless, the total sodium exposure estimated using INTERSALT formulae was not associated with the gastric cancer risk in our study, likely due to dilution effects that have been previously described in studies comparing sodium exposure based

on spot vs. 24-h urine samples [26, 27]. After excluding gastric cancer cases occurring in the first year of follow-up, however, these associations became considerably stronger, suggesting presence of reverse causality (.e.g., persons with gastric symptoms preceding cancer diagnosis might have reduced their salt intake) [28].

Our findings on “always adding salt to food” and gastric cancer are in line with the findings of a recent pooled analyses of 25 case-control studies conducted in America, Asia and several European countries [29], which showed a positive associations between added salt and gastric cancer. They are also in line with findings from a recent meta-analysis of prospective studies showing higher gastric cancer risk among Asian populations with higher salt intake [30]. However, in contrast to our study, two previous smaller studies from Europe did not show associations between total salt intake derived from dietary questionnaires and gastric cancer risk [31, 32]. This difference may be in part explained by the difficulty of measuring total salt intake by dietary questionnaires [27]. In turn, our study suggests that adding salt to food is an eating behavior that may be a very good proxy of habitual salt intake and less prone to day-to-day variation, as also indicated by the graded association between added salt intake and urinary sodium. In addition, “always adding salt to food” may serve as a simple indicator for estimating excessive sodium in large populations. It is also easily convertible to a public health message and may aid in reducing overall sodium intake both on individual and population levels.

While our study based on a large cohort suggests that excessive salt intake is a gastric cancer risk also in non-Asian populations, it has several limitations. Case numbers in our study were not sufficient to evaluate the influence of potential modifiers such as sex, age, ethnicity, *H. pylori* infection or smoking status. *H. pylori* status was ascertained from self-reported and hospital impatient data, and positivity was most probably underestimated. Also, due to the observational nature of our study residual confounding cannot be excluded. Our ancillary analyses on urinary sodium and gastric cancer were restricted to spot urine samples, which have been shown to lead to biased associations with cardiovascular diseases compared to 24-hour urine samples [26, 27]. Also, the case number available for these analyses was rather low. Data on dietary salt intake in the UK Biobank are restricted to a subsample of around 20% of the participants with a limited number of 24-h dietary assessments. Therefore, the case numbers in this subset would not have been sufficient for analyses on gastric cancer risk. Finally, our findings cannot be generalized to the general UK population due to voluntary participation and age restriction of the UK Biobank cohort.

To conclude, our prospective study in a large sample of 471,144 UK adults suggests that routinely adding salt to food is associated with a greater risk of gastric cancer compared to never adding salt to food. While more studies among other non-Asian populations are needed, lower gastric cancer rates may be a co-benefit of salt reduction programs with the main aim to reduce cardiovascular diseases [33]

Table 1
Study sample characteristics at baseline in 2006–2010 by the frequency of adding salt to food (N = 471,144)

	Total	Added Salt Use			
		Rarely/never (N = 261,195)	Sometimes (N = 132,238)	Usually (N = 54,753)	Always (N = 22,958)
Age, years (mean, sd)	56.3 (8.1)	56.3 (8.1)	56.2 (8.1)	56.8 (8.1)	55.7 (8.3)
Sex, male (%)	46.1	44.5	46.5	51.7	48.9
Ethnicity, white (%)	90.5	91.8	89.9	88.3	83.8
Education level, medium/high (%)	56.3	57.6	57.5	54.6	45.0
Townsend deprivation index (mean, sd)	-1.3 (3.1)	-1.5 (3.0)	-1.2 (3.0)	-1.1 (3.2)	-0.2 (3.5)
Alcohol consumption, 16 + grams of ethanol/day (%)	32.3	29.3	33.9	39.9	39.9
Smoking status, previous/current (%)	44.9	40.4	47.2	54.4	59.1
BMI, kg/m^2 (mean, sd)	27.4 (4.8)	27.2 (4.7)	27.6 (4.8)	27.8 (4.8)	28.1 (5.1)
Physical activity, METs hr/week (mean, sd)	35.0 (49.1)	34.7 (47.2)	34.9 (49.3)	35.1 (50.6)	38.9 (62.7)
Use of diuretics, yes (%)	7.6	8.0	7.2	7.1	7.1
H. pylori infection, yes (%)	0.3	0.3	0.3	0.4	0.4
Multimorbidity, 2 or more (%)	29.7	29.3	29.4	30.9	32.4
Spot urine sodium excretion (mmol/L) (mean, sd)	77.8 (44.6)	73.3 (42.7)	80.8 (45.0)	86.0 (46.9)	92.7 (84.7)
Estimated 24h sodium excretion using INTERSALT formulae (g/d) (mean, sd)	3.0 (2.9)	2.9 (7.7)	3.0 (8.1)	3.1 (8.4)	3.2 (8.5)

Table 2
Hazard ratios and 95% confidence intervals for the frequency of adding salt to food and the risk of gastric cancer (N = 471,144)

	Never/rarely	Sometimes	Usually	Always	P-trend
Cases, n	322	175	90	53	
Person-years	2746652.9	1390018.7	573214.5	238256.2	
Sex and ethnicity-adjusted	1 (ref)	1.07 (0.89, 1.28)	1.21 (0.96, 1.53)	1.88 (1.41, 2.52)	0.0002
Multivariable-adjusted[a]	1 (ref)	0.99 (0.82, 1.19)	1.09 (0.86, 1.38)	1.39 (1.02, 1.88)	0.09
Multivariable-adjusted + dietary factors[b]	1 (ref)	0.99 (0.82, 1.19)	1.09 (0.86, 1.39)	1.41 (1.04, 1.91)	0.08
Excluding cases in the first year of follow-up[c]	1 (ref)	0.95 (0.78, 1.16)	1.07 (0.83, 1.37)	1.45 (1.06, 1.98)	0.08
Excluding multimorbidity cases[d]	1 (ref)	1.00 (0.79, 1.28)	1.18 (0.88, 1.58)	1.30 (0.87, 1.94)	0.15

[a] Sex, ethnicity, education level (low, medium, high), Townsend deprivation index (in quintiles), smoking status (never, previous, current), alcohol consumption, physical activity (in MET hours/week), BMI (continuous), use of diuretics (yes/no), multimorbidity (0, 1, 2, 3+); N = 450,080; N_{cases}=619.

[b] Also adjusted for dietary factors at baseline (frequency of consumption of beef, processed meat, pork, fresh fruit, salad/raw vegetables, and cooked vegetables), N = 450,080 ; N_{cases}=619.

[c] Excluding gastric cancer cases occurring in the first year of follow-up. N = 450,042, ; N_{cases}=581.

[d] Excluding multimorbidity cases at baseline (i.e. persons with 2 or more coexisting disease conditions) in multivariable models. N = 316,872; N_{cases}=391.

Table 3
Hazard ratios and 95% confidence intervals of INTERSALT formula-estimated 24h urinary sodium and gastric cancer risk (N = 453,309)

Estimation method	T1[a]	T2	T3	P-trend
Cases, n	139	144	329	
Sex and ethnicity-adjusted	1 (ref)	0.98 (0.74, 1.29)	1.40 (1.03, 1.90)	0.001
Multivariable-adjusted[b]	1 (ref)	0.94 (0.71, 1.24)	1.27 (0.93, 1.74)	0.07
Excluding cases in the first year of follow-up[c]	1 (ref)	0.97 (0.72, 1.29)	1.39 (1.01, 1.93)	0.01
Excluding multimorbidity cases[d]	1 (ref)	0.89 (0.62, 1.27)	1.19 (0.80, 1.76)	0.16

[a] Tertile of estimated 24h urinary sodium excretion

[b] Sex, ethnicity, education level (low, medium, high), Townsend deprivation index (in quintiles), smoking status (never, previous, current), alcohol consumption, physical activity (in MET hours/week), use of diuretics (yes/no), and multimorbidity (0, 1, 2, 3+), N = 434,515; N_{cases}=594.

[c] Excluding gastric cancer cases occurring in the first year of follow-up, N = 434,479; N_{cases}=558.

[d] Excluding multimorbidity cases at baseline in multivariable models. N = 306,645; N_{cases}=378.

Declarations

The UK Biobank study was approved by the National Health Service (NHS) North West Multi-centre Research Ethics Committee. All participants provided written informed consent at recruitment.

Conflict of Interest: None declared

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Figures

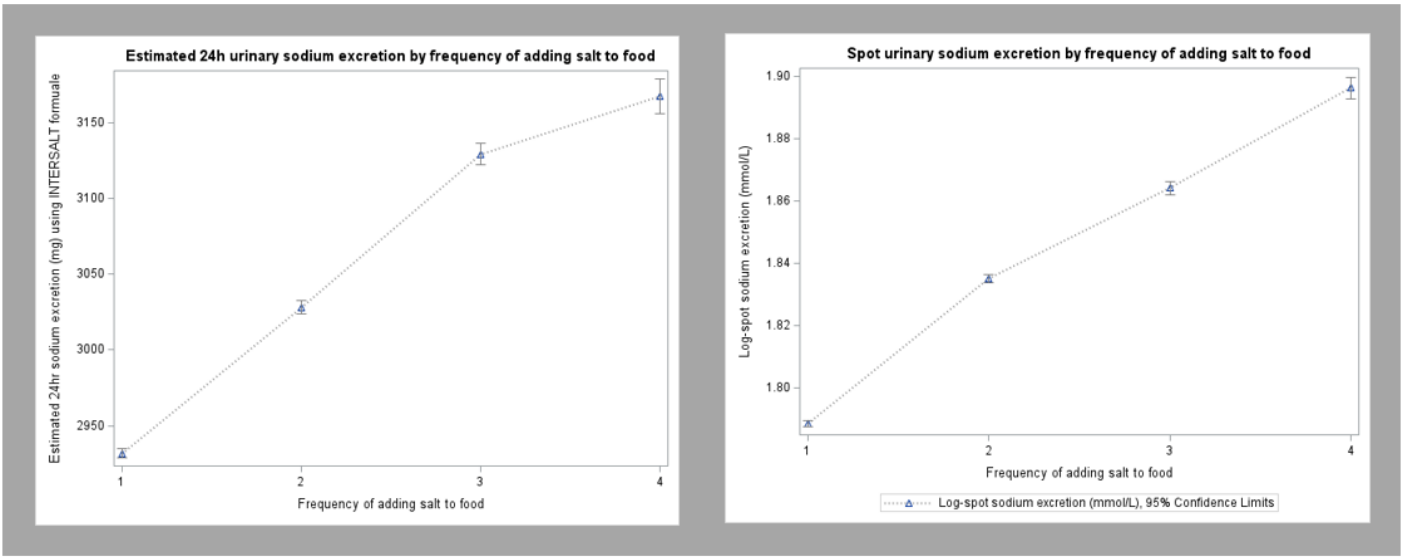

Figure 1

Association between 24-h estimated urinary sodium and the frequency of adding salt to food[a]

[a] Frequency of adding salt to food: 1- never/rarely; 2-sometimes; 3-usually; 4-always. All associations were statistically significant, with p-values for linear trend across categories of adding salt <0.001.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementalfigure1Studyflowchartv1112.docx