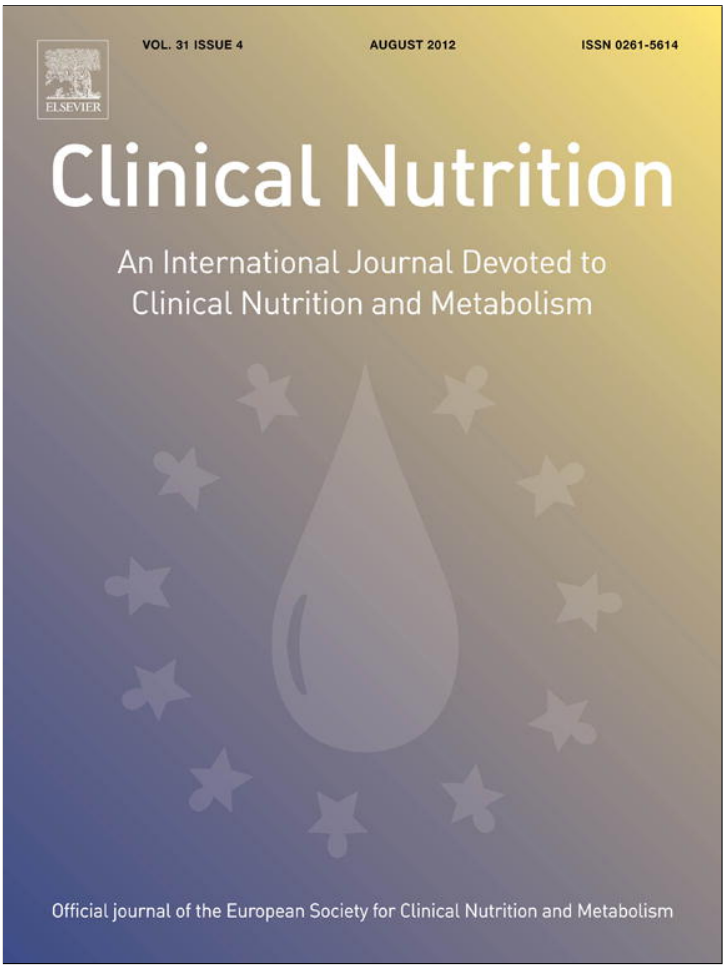

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Original article

Habitual salt intake and risk of gastric cancer: A meta-analysis of prospective studies

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SUMMARY

Background & aims: Systematic reviews of case–control studies evaluating the relationship between dietary salt intake and gastric cancer showed a positive association, however a quantitative analysis of longitudinal cohort studies is lacking. Therefore, we carried out a meta-analysis to assess the association between habitual salt intake and risk of gastric cancer in prospective studies.
Methods: We performed a systematic search of published articles (1966–2010). Criteria for inclusion were: original articles, prospective adult population studies, assessment of salt intake as baseline exposure and of gastric cancer as outcome, follow-up of at least 4 years, indication of number of participants exposed and events across different salt intake categories.
Results: Seven studies (10 cohorts) met the inclusion criteria (268 718 participants, 1474 events, follow-up 6–15 years). In the pooled analysis, "high" and "moderately high" vs "low" salt intake were both associated with increased risk of gastric cancer (RR = 1.68 [95% C.I. 1.17–2.41], $p = 0.005$ and respectively 1.41 [1.03–1.93], $p = 0.032$), with no evidence of publication bias. The association was stronger in the Japanese population and higher consumption of selected salt-rich foods was also associated with greater risk. Meta-regression analyses did not detect specific sources of heterogeneity.
Conclusions: Dietary salt intake was directly associated with risk of gastric cancer in prospective population studies, with progressively increasing risk across consumption levels.

1. Introduction

Excess dietary salt intake is a worldwide hazard to community health being causally related to such epidemic disorders as hypertension,[1,2] cardiovascular disease,[3] renal dysfunction,[4] nephrolithiasis[5] and osteoporosis.[6] Stomach cancer is still a common neoplasia and an important, at least partly, preventable public health problem.[7–9] Given that high salt intake has been associated with Helicobacter pylori infection,[10] as promoter of damage of gastric mucosa,[11] hypergastrinemia and cell proliferation,[12] numerous case–control studies in the past investigated the relationship between salt consumption and risk of gastric cancer (ref. 13 for review) and, most often, reported a positive statistical association. None of these studies had a nested case–control design and altogether they do not allow to make inferences about the possibility of a causal association. In addition, however, several prospective studies have been performed to evaluate the relationship between salt or salted foods and risk of stomach cancer. In general, the detection of statistical associations in prospective studies provides stronger support to the possibility of a cause–effect relationship; however, in the case of excess salt intake and risk of gastric cancer the cohort studies available did not show consistent results.[13] For this reason, we carried out a systematic review and meta-analysis of these studies to evaluate the association between habitual levels of dietary salt intake and risk of gastric cancer and to obtain an estimate of risk.

2. Methods

2.1. Data sources and searches

This meta-analysis was planned, conducted and reported according to the PRISMA statement[14] (Appendix Table 1). We performed a systematic search for publications using MEDLINE (from 1966 to December 2010), and the Cochrane Library. The search strategy used the expressions: *Salt, Salty, Salted, Sodium, Diet, Dietary, Food, Snack* AND *Stomach cancer, Gastric cancer, Helicobacter pylori, HP, Chronic atrophic gastritis, adenomatous polyps*, intestinal

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; MeSH, Medical Subject Headings; RR, Relative Risk.

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metaplasia, dysplasia or combinations thereof, either in medical subject headings (MeSH) or in the title/abstract, with no restrictions (Appendix Table 2). Further information was retrieved through a manual search of references from recent reviews and relevant published original studies.

2.2. Study selection

Two reviewers (GR and RI) independently extracted the data. Discrepancies about inclusion of studies and interpretation of data were resolved in conference with arbitration by a third investigator (LD), and consensus was reached after discussion. To be included in the meta-analysis a published study had to meet the following criteria: (a) original article, (b) prospective design, (c) adult population, (d) assessment of salt/sodium intake as baseline exposure, (e) diagnosis of gastric cancer determined prospectively as outcome (gastric cancer incidence and/or mortality rate), (f) indication of the number of participants exposed and the rate or number of events in different categories of salt/sodium intake, (g) assessment of relative risk (RR) or hazard ratio (HR) for different salt/sodium intake categories, (h) follow-up of at least 4 years (mean or median).

2.3. Data extraction and quality assessment

The following characteristics of the identified studies and respective populations were recorded: publication reference, total number of participants, gender, country, age (mean and/or range), recruitment time, follow-up (years), outcome reported (gastric cancer events and/or mortality rate), outcome assessment method, sodium intake assessment method, number (rate) of events, and level of salt/sodium intake or of salty food consumption in different categories.

Categorization of habitual salt intake in the different studies was provided either in terms of total daily dietary salt/sodium intake or in terms of consumption of particular salty foods or both. For our analysis, we used, whenever possible, the outcome provided for total dietary salt/sodium intake; nevertheless, we referred to consumption of salty foods when this was the only item available. All studies stratified salt/sodium intake or consumption of salty foods through multiple (3–5) categories and reported estimates of risk for each category relative to the lowest one, referred to as reference intake.

For all these studies we performed separate meta-analyses to evaluate the relative risk of an event in the highest ("high" intake) and respectively the intermediate ("moderately high" intake) category vs the lowest intake category (Table 2). The same type of categorization was adopted for additional analyses of the effects of specific salt-rich foods (namely, pickled foods, salted fish, processed meat and miso-soup)

The quality of the studies included in the meta-analysis was evaluated by the Newcastle-Ottawa Scale.[15] A greater score was considered to be an indicator of better quality on a scale of 9.

2.4. Statistical analysis

Relative risks or hazard ratios were extracted from the selected publications and their standard errors were calculated from the respective confidence intervals (C.I.). The value from each study and the corresponding standard error were transformed into their natural logarithms to stabilize the variances and to normalize their distribution. The pooled RR [and 95% C.I.] was estimated using a random effect model, weighting for the inverse of the variance.[16] The heterogeneity among studies was tested.[17] Funnel plot asymmetry was used to detect publication bias and the Egger's regression test was applied to measure funnel plot asymmetry.[18,19] The influence of individual cohorts was examined by sensitivity analysis. Subgroup and meta-regression analyses were used to identify associations between risk of gastric cancer and relevant study characteristics (participants' gender, country of origin, year of publication, duration of follow-up, age, outcomes) as possible sources of heterogeneity. Further details of the method have been previously described.[20]

All statistical analyses were performed using MIX software version 1.7[21] and the Stata Corp. software version 9.1 for meta-regression analysis.[22]

3. Results

Of a total of 7352 publications retrieved (Fig. 1), 9 studies were identified that met the inclusion criteria. Since three of these studies referred to the same cohort (JPHC study),[23–25] we included the one having the highest number of participants and events, and reporting histological diagnosis, separate analysis of male and female cohorts, longest follow-up duration and best salt intake categorization.[23]Thus, eventually 7 studies were used for the meta-analysis, providing suitable data on 10 cohorts (Table 1).[23,26–31] Additional analyses were carried out of the effect of salt-rich foods on the rate of gastric cancer, with the inclusion of a total of 14 studies (Appendix Table 3).[23,26,27,32–42]

Table 1
Characteristics of the prospective studies included in the meta-analysis.

First author (ref)	Year	Country	Gender	Age (yrs) mean [range]	Recruitment time	Follow-up (yrs)	Outcome assessment	Sodium intake assessment	Quality score
Galanis [26]	1998	USA (Hawaii)	Men Women	46.4 [−]	1975–1980	14.8[a]	Record linkage with cancer registries Hawaii Tumor Registry	Questionnaire (13 items)	7
Ngoan [27]	2002	Japan	Men Women	52.1 [15–96] 53.1 [20–92]	1986–1989	8.8[a]	Histology	Questionnaire (254 items)	7
Van den Brandt [28]	2003	The Netherlands	Total	− [55–69]	1986	6.3	Record linkage with Duch Cancer Registry and pathology registry	Questionnaire (150 items)	7
Tsugane [23]	2004	Japan	Men Women	49.4 [40–59] 49.6 [40–59]	1990–1992	11	Cancer registries for JPHC (ICD-O), death certificates, and histological confirmation	Questionnaire (27 items)	7
Kurosawa [29]	2006	Japan	Total	− [30+]	1989	11	Family and Registration Law	Questionaire (29 items)	7
Shikata [30]	2006	Japan	Total	57.9 [40+]	1988	14	Histology	Questionnaire (70 items)	7
Sjödahl [31]	2008	Norway	Total	49.0 [−]	1984–1986	15.4[a]	Cancer Registry of Norway (ICD-7) and histological confirmation	Questionnaire	7

[a] Mean follow-up.

Table 2
Detailed outcome of the studies.

First author, year (ref)	Participants'gender	Study population (n)	Gastric cancer (n)		Type of estimate of habitual sodium intake	Comparisons	Factors controlled for in multivariate analysis
			Events	Mortality			
Galanis, 1998 [26]	Men Women	5610 6297	64 44	–	Salted food consumption (miso-soup, pickled vegetables and dried fish)	None 1–3 times/wk ≥4 times for wk	Age, education, Japanese place of birth (for men were also adjusted for smoking and alcohol intake).
Ngoan, 2002 [27]	Men Women	5917 7333	–	77 39	Salted food consumption	Low intake Medium intake High intake	Age, gender, smoking, processed meat, liver, cooking or salad oil, suimono and pickled fruit.
Van den Brandt, 2003[28]	Total	120 852	282	–	Total salt intake	Q1 (g/day) Q3 Q5	Age, gender, smoking, education, family history of stomach disorders and stomach cancer.
Tsugane, 2004[23]	Men Women	18 684 20 381	358 128	–	Total salt intake	Q1 (g/day) Q3 Q5	Age, smoking, fruit and non-green – yellow vegetable intake.
Kurosawa, 2006[29]	Total	8035	–	76	Highly salted food consumption (pickled vegetable, foods deep-boiled in soy sauce)	Low Intermediate High	Age, gender.
Shikata, 2006 [30]	Total	2476	93	–	Total salt intake	<10 g/day 10–12.9 ≥16	Age, gender, Helicobacter pylori infection, atrophic gastritis, history of peptic ulcer, family history of cancer, BMI, diabetes mellitus, total cholesterol, physical activity, alcohol intake, smoking and dietary factors (intake of total energy, total protein, carbohydrate, B1-B2-C vitamin and dietary fiber).
Sjödahl, 2008[31]	Total	73 133	313	–	Total salt intake	Low intake Moderate intake High intake	Age, smoking, alcohol intake, physical activity and occupation.

3.1. Characteristics of the study cohorts

The relevant features of the 7 studies and the 10 cohorts included in the meta-analysis are reported in Table 1. Overall, the meta-analysis involved 268 718 participants from 4 countries (4 studies from Japan, 1 from USA, The Netherlands and Norway). All the studies recruited both male and female participants but only 3 reported separate outcomes for men and women.[23,26,27] Five studies reported gastric cancer events (fatal and/or non fatal), while two only fatal outcomes. In all studies, salt intake was assessed by dietary surveys using specific questionnaires. The overall number of gastric cancer events was 1474, whereas the number of fatal events was 192.

3.2. "High" salt intake and risk of gastric cancer

There were 10 cohorts available to evaluate the risk of gastric cancer associated with "high" versus low salt intake. The weighted

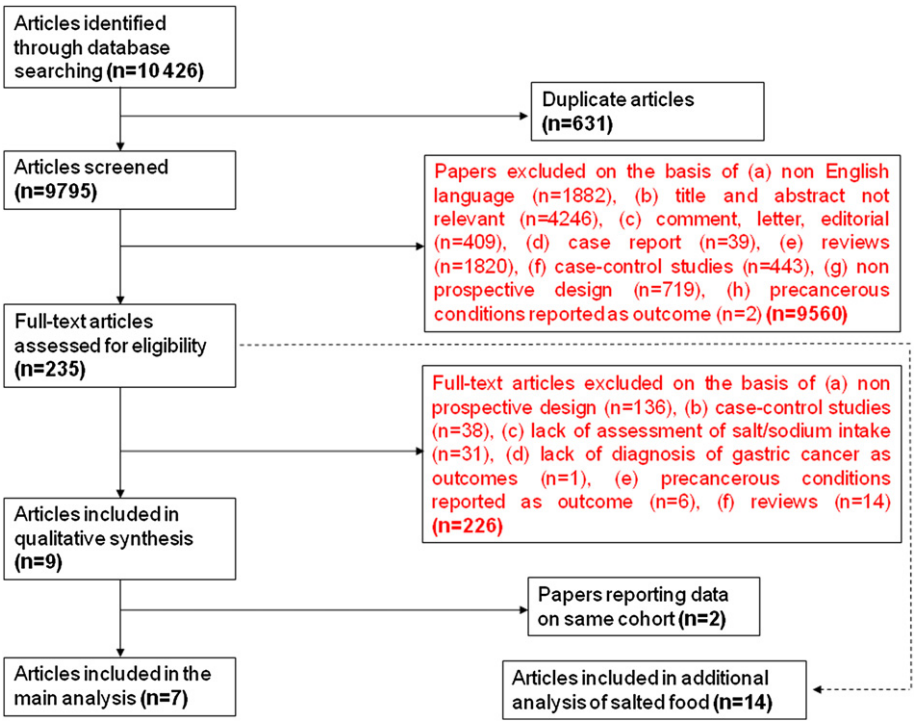

Fig. 1. Stepwise procedure for selection of the studies. Flowchart indicating the results of the systematic review with inclusions and exclusions.

average follow-up time was 10.4 years (range 6–15). Detailed figures on population size, incident gastric cancer and levels of salt/sodium intake of the 10 cohorts included in the analysis are given in Table 2 (overall 268 718 participants and 1474 events).[23,26–31] The results of the pooled analyses are shown in Fig. 2A in the form of a forest plot. "High" salt intake was associated with a 68% greater risk of gastric cancer compared with low intake (RR = 1.68 [95% C.I. 1.17–2.41]; $z = 2.79$; $P = 0.005$). There was significant heterogeneity between studies ($Q = 31.0$, $P < 0.01$; $I^2 = 71\%$ [95% C.I. 45–85]), but no evidence of publication bias by the Egger's test ($P = 0.46$). As shown in Fig. 1 for the individual cohorts included in the analysis, a trend toward a direct association between salt intake and gastric cancer risk was detected in 7 cohorts and was statistically significant in 3 of them. A non significant opposite trend was observed in only one cohort. Sensitivity analysis showed that the risk of gastric cancer did not vary substantially with the exclusion of any individual study.

Further analyses were carried out to check for potential sources of heterogeneity that might explain the association between dietary salt intake and gastric cancer events. Subgroup analysis was used for categorical variables and meta-regression for continuous variables.

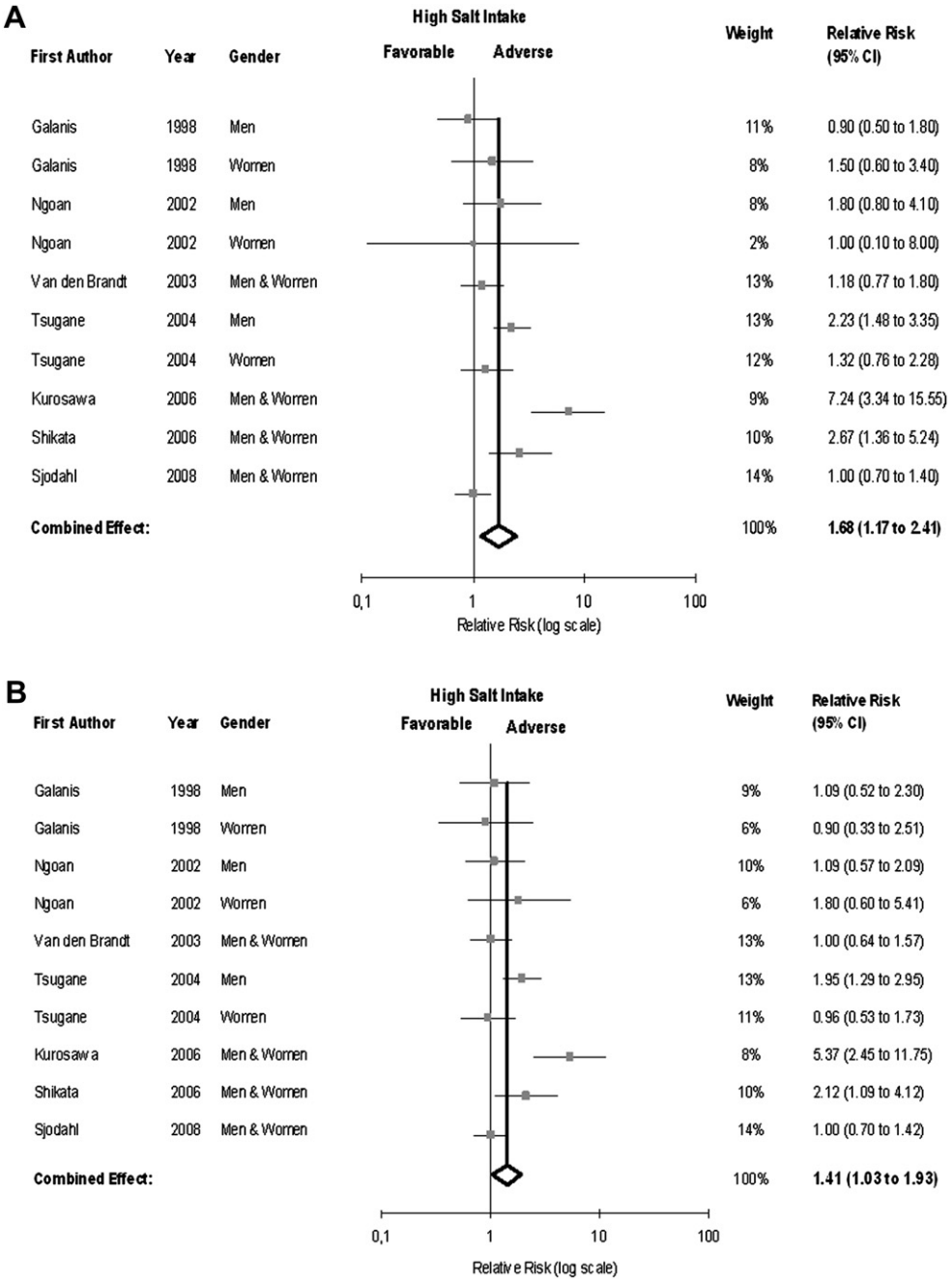

Fig. 2. A. "High" Salt intake and risk of gastric Cancer. Forest plot of the risk of gastric cancer associated with "high" salt intake compared to "low" salt intake in 10 population cohorts from 7 published prospective studies. Total population, $n = 268\,718$; events, $n = 1474$. Results are expressed as relative risk (RR) and 95% confidence intervals (95% C.I.). Fig. 2B. "Moderately High" salt intake and risk of gastric cancer. Forest plot of the risk of gastric cancer associated with "moderately high" salt intake compared to "low" salt intake in 10 population cohorts from 7 published prospective studies. Total population, $n = 268\,718$; events, $n = 1474$. Results are expressed as relative risk (RR) and 95% confidence intervals (95% C.I.).

3.2.1. Subgroup analysis

The relationship between salt intake and risk of gastric cancer was not significantly different in men[23,26,27] (RR = 1.58 [95% C.I. 0.89–2.81]) and women[23,26,27] (RR = 1.35 [95% C.I. 0.86–2.13]) (P for heterogeneity: $p = 0.66$). With regard to the geographic location, "high" salt intake was a better predictor of the risk of gastric cancer in Japanese[23,27,29,30] (RR = 2.35 [95% C.I. 1.46–3.79) than in North American[26] (RR = 1.08 [95% C.I. 0.65–1.82]) and European populations[28,31] (RR = 1.08 [95% C.I. 0.81–1.43]) (P for heterogeneity = 0.026). Separate analysis of the studies reporting RR estimates for total events confirmed the direct association between "high" salt consumption and risk of gastric cancer (7 cohorts, pooled RR = 1.42 [95% C.I. 1.04–1.92], $P = 0.02$; $Q = 13.9$, $P = 0.03$, $I^2 = 57\%$ [0–81]).[23,26,28,30,31] An even stronger trend in the same direction was observed in the analysis of the studies reporting the effect on mortality for gastric cancer but in this case the association did not reach statistical significance (3 cohorts, RR = 2.89 [95% C.I. 0.88–9.37], $P = 0.079$; $Q = 7.2$, $P = 0.03$, $I^2 = 72\%$ [6–92]).[27,29]

3.2.2. Meta-regression analysis

Meta-regression analysis indicated no influence of the year of publication ($P = 0.33$), length of follow-up ($P = 0.54$), and the population average age ($P = 0.43$) on the association between salt intake and risk of gastric cancer.

3.3. "Moderately high" salt intake and risk of gastric cancer

We next assessed the effect of "moderately high" salt intake on incident gastric cancer. In the pooled analysis (10 cohorts; 268 718 participants and 1474 events),[23,26–31] "moderately high" salt intake was significantly associated with a 41% greater risk of gastric cancer (RR = 1.41 [95% C.I. 1.03–1.93]; $z = 2.14$; $P = 0.032$). There was heterogeneity between studies ($Q = 24.1$, $P = 0.04$; $I^2 = 63\%$ [26–81]), but no evidence of publication bias by the Egger's test ($P = 0.43$). The evaluation of individual studies showed a trend toward a direct association between salt consumption and gastric cancer risk in 6 cohorts with significantly higher risk in three, whereas a non significant opposite trend was observed in 2 cohorts (Fig. 2B).

3.3.1. Dose-response analysis

Upon analysis of the trend across salt consumption categories, a progressive significant increase in risk of gastric cancer was observed stepping from "moderately high" (RR = 1.41) to "high" salt intake (RR = 1.68) in comparison with "low" salt consumption (P for trend = 0.034).

3.4. Salt-rich foods and risk of gastric cancer

We carried out additional analyses to evaluate the possible effect of selected salt-rich foods on risk of gastric cancer. The relevant characteristics of the studies included in these analyses are reported in Appendix Tables 3 and 4. The results of these analyses are reported in Fig. 3.

3.4.1. Pickled foods

The pooled RR for "high" pickled food consumption (11 cohorts)[23,26,27,32,34,39,40] showed a positive and statistically significant association with rate of gastric cancer (RR = 1.27 [95% C.I. 1.09–1.49]; $P = 0.002$), with no significant heterogeneity between studies ($Q = 13.4$, $P = 0.20$, $I^2 = 25\%$ [0–63]) (Fig. 3A).

3.4.2. Salted fish

Also "high" salted fish consumption (13 cohorts)[23,26,27,33,34,36,38,40] was significantly associated with greater risk of gastric cancer (RR = 1.24 [95% C.I. 1.03–1.50]; $P = 0.022$), without evidence of heterogeneity ($Q = 8.4$, $P = 0.75$, $I^2 = 0\%$ [0–57]) (Fig. 3B).

3.4.3. Processed meat

The analysis of processed meat consumption (7 cohorts)[26,27,37,41,42] indicated a statistically significant association between "high" consumption and incident gastric cancer (RR = 1.24 [95% C.I. 1.06–1.46]; $P = 0.009$) without evidence of heterogeneity ($Q = 7.6$, $P = 0.27$, $I^2 = 21\%$ [0–64]) (Fig. 3C).

3.4.4. Miso-soup

In this analysis, there was no significant association between "high" consumption and risk of gastric cancer (12 cohorts)[23,26,27,32,35,38–40] (RR = 1.05 [95% C.I. 0.88–1.25]; $P = 0.59$; heterogeneity: $Q = 15.0$, $P = 0.18$, $I^2 = 27\%$ [0–63]) (Fig. 3D).

4. Discussion

The present meta-analysis assessed the relationship between habitual dietary salt intake and risk of gastric cancer in an overall sample of nearly 270 000 individuals from 7 prospective studies. The main finding was the demonstration of a graded positive association between salt consumption and incidence of gastric cancer. Our pooled estimates indicate that habitual "high" and "moderately high" salt intake are associated with 68% and 41% greater risk of gastric cancer, respectively, compared with "low" salt consumption.

The relationship was not significantly different in men and women, and likewise was not affected by the length of follow-up, the year of publication, and the participants' age at enrollment. Salt consumption was a particularly strong predictor of gastric cancer in the studies carried out in Japanese populations. In addition to the main finding, we observed that the estimated risk of gastric cancer was greater in individuals who reported to be habitual eaters of salt-rich foods: in particular, elevated consumption of pickled foods, salted fish and processed meat were associated with respectively 27%, 24% and 24% greater risk of gastric cancer.

A recently published study, including nearly 80 000 participants belonging to the JPHC cohort, confirmed a similar positive trend between salt intake and gastric cancer risk, but this relation was not statistically significant.[25] This study was not included in the present meta-analysis because it had a short follow-up, did not report histological diagnosis and did not perform separate analysis for male and female individuals, at variance with the report by Tsugane and colleagues on the same population.[23] We performed however an additional analysis that included the results of the JPHC cohort reported by Takachi and co-workers in place of the report on the same cohort by Tsugane et al (included in the main analysis), and we found that its results confirmed the same positive trend ("high" vs "low" sodium intake: RR = 1.54 [95% C.I. 1.06–2.24]; $P = 0.024$).

The results of the large number of case–control studies carried out in the past on the relationship between salt intake and gastric cancer, in the large majority in favor of a positive association, are in keeping with the results of our meta-analysis of prospective studies and in fact suggest a possible association also in American[43,44] and European populations.[45–47] A consensus document of the World Cancer Research Fund International in 2007 supported a significant relationship between salted foods consumption and risk of gastric cancer based on a meta-analysis of these case–control studies.[48] In addition, the authors reported the results of a meta-analysis of two

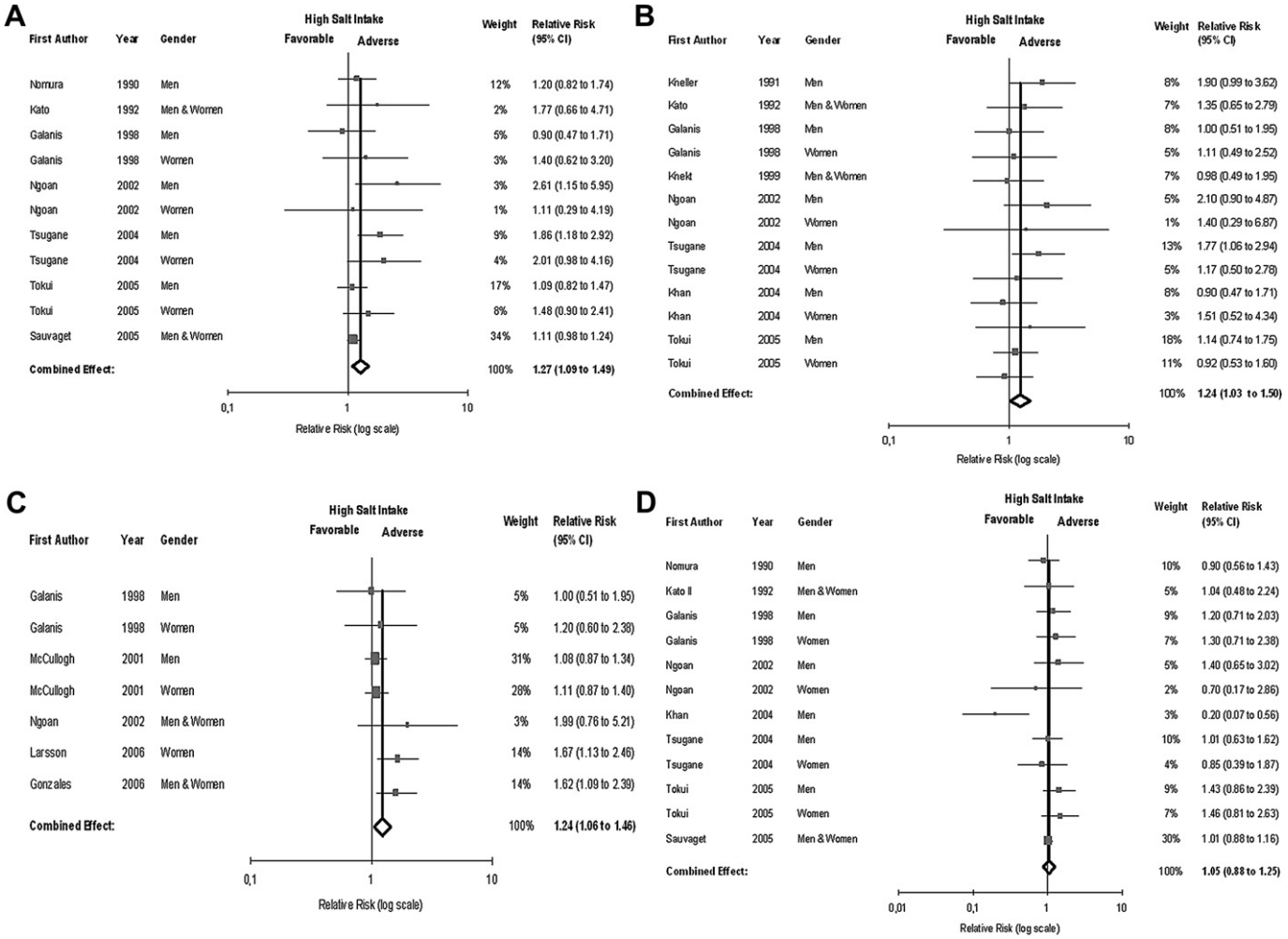

Fig. 3. Salt-rich foods intake and risk of gastric cancer. A. Pickled foods: forest plot of the risk of gastric cancer associated with "high" pickled foods intake compared to "low" intake in 11 population cohorts from 7 published prospective studies. Total population, $n = 242\,568$; events, $n = 2858$. B. Salted fish: forest plot of the risk of gastric cancer associated with "high" salted fish intake compared to "low" intake in 13 population cohorts from 8 published prospective studies. Total population, $n = 209\,704$; events, $n = 1447$. C. Processed meat: forest plot of the risk of gastric cancer associated with "high" processed meat intake compared to "low" intake in 7 population cohorts from 5 published prospective studies. Total population, $n = 1\,578\,092$; events, $n = 2002$. D. Miso-soup: forest plot of the risk of gastric cancer associated with "high" miso-soup intake compared to "low" intake in 12 population cohorts from 8 published prospective studies. Total population, $n = 249\,931$; events, $n = 3022$. Results are expressed as relative risk (RR) and 95% confidence intervals (95% C.I.).

prospective studies on the effect of habitual total salt intake and of a separate meta-analysis of three other studies on the effect of salted foods on the risk of gastric cancer, both of them supporting a positive association.

Recently, a meta-analysis has also been published of seven studies that investigated the relationship between salt intake and gastric intestinal metaplasia.[49] The authors reported separate results for salted food consumption, preference for salted foods (or use of table salt) and urinary sodium excretion, and included in the analysis cohort, case–control and cross-sectional studies. The analysis detected a positive but not statistically significant trend and was affected by large between-study heterogeneity.

Finally, our study demonstrated a statistically significant positive association between the consumption of selected salt-rich foods and rate of gastric cancer. In particular, the results on the relationship between processed meat intake and risk of gastric cancer confirm and strengthen the results of a previous meta-analysis, which indicated a non significant trend in the same direction being affected by a large between studies heterogeneity.[50]

4.1. Strengths and limitations

Strengths of our study were the relatively large number of participants and events, the inclusion of only prospective cohort studies, the adoption of precise pre-determined criteria for inclusion, the evaluation of both fatal and non fatal occurrence of gastric cancer, and the evidence of no publication bias. The finding of a "graded" association between habitual salt consumption and risk of gastric cancer increases the strength of our finding.

Our meta-analysis however also had limitations. There was significant heterogeneity between studies and large differences with regard to sample size, length of observation, number of events, assessment of outcomes, categorization of salt intake and salt exposure, and adjustment for potential confounders. In particular, only one study adjusted for *Helicobacter pylori* infection (30) but indeed, being Helicobacter pylori infection possibly along the pathogenetic pathway conducting from excess salt intake to development of gastric cancer, this might be seen as an "over-adjustment". Four out of the seven studies included in the meta-analysis were performed in Japan and, indeed, the geographic

location of the studies was the only source of heterogeneity identified as statistically significant. An important limitation was the presumably inaccurate assessment of habitual sodium intake in as much as none of the available studies used 24-h urinary sodium excretion as indicator of salt intake. In general, these methodological inaccuracies may have conceivably led to a reduced statistical power in detecting a true biological association between dietary salt consumption and occurrence of gastric cancer and actually to underestimate the true effect of excess salt consumption on the risk of gastric cancer. This notwithstanding, the evidence in favor of an adverse effect of excess salt intake on gastric cancer rate was strong, albeit limited to the Japanese population.

Most important, the possible influence of unknown confounders on the association detected cannot be completely ruled out since age was the only potential confounder accounted for by all the studies included in the meta-analysis. In particular, it is to be noted that in a prospective study in the Netherlands[28] consumption of high salt foods was found to be associated with an increased intake of nitrites, which are known to exert a mutagenic effect in the stomach after conversion to nitrosamines.[53] Thus, possible confounding by nitrite intake should be ideally taken into account in future studies.

4.2. Potential mechanisms

A number of experimental studies provide possible mechanistic explanations for a causal role of an elevated salt intake on the risk of gastric cancer. High intra-gastric sodium concentrations were shown to cause mucosal damage and inflammation,[51] which in turn has been reported to increase cell proliferation and endogenous mutations.[12,52] High sodium intake appears to change the viscosity of the protective mucous barrier[11]and to increase the colonization by *H. pylori*, a recognized risk factor for gastric cancer.[10]

4.3. Public health implications and future research needs

Gastric cancer remains one of the most common forms of cancer worldwide with approximately 870 000 new cases[54,55] accounting for about 9.9 percent of new cancers.[56] The mortality from this form of cancer remains high with more than 628 000 deaths (12.1%) worldwide, equally represented in developed and developing countries.[57] Whilst the worldwide incidence of gastric cancer has declined rapidly over the recent few decades, in particular in Western countries, in China and other countries in East Asia the decline has been less substantial than for other countries. Actually, an increased incidence has been observed in oldest and youngest age groups.[58] Moreover, the age of onset of developing gastric cancer in the Chinese population is younger than that in the West, and this may signal the effect of new environmental factors.

A population reduction in salt intake is recognized as a global priority for a highly cost-effective prevention of the epidemic of cardiovascular disease both in developed and developing countries.[59–61] Although our results do not conclusively prove a causal relationship between excess salt intake and risk of gastric cancer, they do suggest the potential for further benefit by this policy in addition to its effects on cardiovascular morbidity and mortality.[62]

Future research should focus on deeper evaluation of the mechanisms of the observed association and of its actual strength in non oriental populations.

Financial disclosures

The study was not supported by external funding.

Contribution

LD contributed to the systematic review and to the data extraction, performed the analysis, interpreted the results and drafted the manuscript. GR and RI contributed to the systematic review and to the data extraction. FPC contributed to the systematic review, interpretation of results and to the revision of the manuscript. PS conceived the study aims and design, contributed to the systematic review, interpreted the results and drafted the manuscript.

Declaration of conflicts of interest

FPC is unpaid member of C.A.S.H, W.A.S.H., unpaid technical advisor to the WHO and the PAHO and Member of the Executive Committee and Trustee of the British Hypertension Society. The publication does not necessarily represent the decisions or the stated policy of WHO and the designations employed and the presentation of the material do not imply the expression of any opinion on the part of WHO. PS is unpaid member of W.A.S.H. and the scientific coordinator of the Interdisciplinary Working Group for Reduction of Salt Intake in Italy (GIRCSI). The remaining authors do not disclose any conflict of interest.

Appendix

Table 1
The PRISMA checklist.

1. Title – The report is identified as a systematic review and a meta-analysis.
2. Structure summary – The structured abstract includes Background, Methods and Findings, and Conclusions.
3. Rationale – Described in the Introduction.
4. Objectives – Stated in the Introduction.
5. Protocol and Registration – The protocol is described in the Methods. Registration does not apply.
6. Eligibility criteria – They are defined in the Methods.
7. Information sources – Described in the Methods.
8. Search – Described in the Methods and Appendix Table 2.
9. Study selection - Described in the Methods and Fig. 1.
10. Data collection process – Described in the Methods.
11. Data items – Described in Methods and summarized in Table 1 and Table 2.
12. Risk of bias in individual studies – We explored heterogeneity with a variety of methods (Methods), including quality of study. Randomization does not apply given the prospective nature of the studies.
13. Summary measures – Risk Ratio.
14. Planned methods of analysis – Described in Statistical Analysis.
15. Risk of bias across studies – Described in Statistical Analysis and reported in detail in Results.
16. Additional analyses – Sensitivity analysis, subgroup analysis, and meta-regression analysis.
17. Study selection – see Flow diagram in Fig. 1.
18. Study characteristics – shown in Table 1 and Appendix Table 3.
19. Risk of bias within studies – see 12.
20. Results of individual studies – shown in Figs. 2 and 3.
21. Syntheses of results – shown in Results, Fig. 2, and Fig. 3.
22. Risk of bias across studies – see 15.
23. Additional analyses – results reported in Fig. 3 and in Results.
24. Summary of evidence – stated in Discussion.
25. Limitations – addressed in Discussion.
26. Conclusion – addressed in Discussion.
27. Funding – not applicable in this instance.

Appendix

Table 2
Search strategy.

1	Salt
2	Salty
3	Salted
4	Sodium
5	Diet
6	Dietary
7	Food*
8	Snack*
9	Bread
10	Miso
11	Pickle*
12	Processed fish
13	Processed meat
14	Salty fish
15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
16	Stomach cancer
17	Gastric cancer
18	Helicobacter pylori
19	HP
20	Chronic atrophic gastritis
21	Adenomatous polyps
22	Intestinal metaplasia
23	Dysplasia
24	16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25	#15 AND #24

Appendix

Table 3
Characteristics of the prospective studies included in the meta-analysis of salted food consumption.

First author (ref)	Year	Country	Gender	Age [range](yrs)	Recruitment time	Follow-up (yrs)	Outcome assessment	Sodium intake assessment	Quality score
Nomura[32]	1990	USA	Men	− [45+]	1965–1968	19	Histology	Questionnaire	6
Kneller[33]	1991	USA	Men	− [35+]	1966–1967	20	Death certificates	Questionnaire (9 categories)	6
Kato[34]	1992	Japan	Total	−	1985	4.4[a]	Histology	Questionnaire (10 items)	7
Kato II[35]	1992	Japan	Total	− [30+]	1985	4.4[a]	Death certificates	Questionnaire (25 items)	7
Galanis[26]	1998	USA	Men Women	46.4 [−]	1975–1980	14.8[a]	Record linkage with cancer registries Hawaii Tumor Registry	Questionnaire (13 items)	7
Knekt[36]	1999	Finland	Total	[15+]	1966–1972	24[b]	Finnish Cancer Registry	Questionnaire (1-year dietary history)	9
McCullogh[37]	2001	USA	Total	−	1982	14	Death certificates	Questionnaire (32 items)	8
Ngoan[27]	2002	Japan	Men Women	52.1 [15–96] 53.1 [20–92]	1986–1989	8.8[a]	Histology	Questionnaire (254 items)	7
Tsugane[23]	2004	Japan	Men Women	49.4 [40–59] 49.6 [40–59]	1990–1992	11	Cancer registries for JPHC (ICD-O), death certificates, and histological confirmation	Questionnaire (27 items)	7
Khan[38]	2004	Japan	Men Women	58.0 [40–97] 57.6 [40–97]	1984–1985	13.8[a] 14.8[a]	Death certificates (ICD-9)	Questionnaire (37 items)	8
Sauvaget[39]	2005	Japan	Total	53.0 [34–98]	1980–1981	20	Japanese family registration system	Questionnaire (22 items)	7
Tokui[40]	2005	Japan	Men Women	− [40–79]	1988–1990	11[b]	Death certificates (ICD-9 and ICD-10)	Questionnaire (33 items)	6
Larsson[41]	2006	Sweden	Women	− [Born 1914–1948]	1987–1990	18	National and regional Swedish Cancer registers	Questionnaire (67 item)	8
Gonzales[42]	2006	Europe	Total	− [35–70]	1992–1998	6.5[a]	Cancer registries (France, Germany, Greece: health insurance records, cancer and pathology hospital registries and active follow-up; 56% validated by histology). Death certificates from regional and national registries	Questionnaire	8

[a] Mean follow-up period.
[b] Max follow-up period.

Appendix

Table 4
Detailed outcome of the studies included in the meta-analysis of salted foods consumption.

First author, year (ref)	Participants	Study population (*n*)	Gastric cancer (*n*)				Factors controlled for in multivariate analysis
			Pickled foods	Salted fish	Processed meat	Miso-soup	
Nomura, 1990[32]	Men	7990	150 (E)	–	–	150 (E)	Age.
Kneller, 1991[33]	Men	17,633	–	72 (M)	–	–	Age, smoking.
Kato, 1992[34]	Total	3914	41 (E)	50 (E)	–	–	Age, gender, residence.
Kato II, 1992[35]	Total	9753	–	–	–	64 (M)	Age, gender.
Galanis, 1998[26]	Men	5610	64 (E)	64 (E)	64 (E)	64 (E)	Age, education, Japanese place of birth (For men were also adjusted for smoking and alcohol intake).
	Women	6297	44 (E)	44 (E)	44 (E)	44 (E)	
Knekt, 1999[36]	Total	9985	–	60 (E)	–	–	Age, gender, municipality, smoking, energy intake.
McCullogh, 2001[37]	Men	970,045	–	–	439 (M)	–	Age, education, smoking, BMI, multivitamin and vitamin C use, aspirin use, race, family history.
	Women				910 (M)	–	
Ngoan, 2002[27]	Men	5917	48 (M)	47 (M)	59 (M)	75 (M)	Age, gender, smoking, processed meat, liver, cooking or salad oil, suimono, pickled foods.
	Women	7333	14 (M)	11 (M)		37 (M)	
Tsugane, 2004[23]	Men	18,684	358 (E)	358 (E)	–	358 (E)	Age, smoking, fruit, non-green − yellow vegetable intake.
	Women	20,381	128 (E)	128 (E)	–	128 (E)	
Khan, 2004[38]	Men	1524	.	36 (M)	–	36 (M)	Age, smoking (women also for health status, health education, health screening).
	Women	1634	.	15 (M)	–	–	
Sauvaget, 2005[39]	Total	55,650	1270 (E)	–	–	1270 (E)	Age, gender, city, radiation dose, smoking, education.
Tokui, 2005[40]	Men	110,792	516 (M)	374 (M)	–	530 (M)	Age.
	Women		225 (M)	188 (M)	–	266 (M)	
Larsson, 2006[41]	Women	61,433	–	–	156 (E)	–	Age, education, BMI, intakes of total energy, alcohol intake, fruits, vegetables.
Gonzales, 2006[42]	Total	521,457	–	–	330 (E)	–	Age, gender, height, weight, education, smoking, smoking, work and leisure physical activity, alcohol intake, energy, vegetable, citrus fruit and non-citrus fruit intake, red meat, poultry, processed meat intakes, center EPIC study.

Abbreviations: E, Events; M, Mortality.

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