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Wu B, Yang D, Yang S, Zhang G. Dietary Salt Intake and Gastric Cancer Risk: A Systematic Review and Meta-Analysis. Front Nutr. 2021;8:801228.

What We Know, Think We Know, or Are Starting to Know

We've gotten pretty salty around here regarding some of the narratives that are popular about sodium and health that abound on social media and in the fitness industry. But we have also exclusively focused on hypertension and cardiovascular disease [CVD]. The backlog in this regard includes:

- Sodium and CVD Webinar.
- Sodium and CVD Long-form Article.
- The SaSS Trial of Sodium and Stroke Deepdive.
- The DASH Diet and Blood Pressure Deepdive.
- The "J-Shaped Curve" in Epidemiology Deepdive.
- More "J-Shaped Curve" Epi Deepdive.
- Bye-bye "J-Shaped Curve" Research Lecture.

If sodium and CVD is a metaphorical dead horse, and science is a flog, it is fair to say that we have been flogging said dead horse.

But what of other health outcomes? Are the potential adverse effects of high sodium diets confined to CVD outcomes?

If you've watched the webinar [linked above], you may have noticed a reference to another outcome: gastric [stomach] cancer. This association was evident from one of the earliest sodium studies, known as 'INTERSALT', which contained from data from 39 cohorts in 24 countries [1]. Sodium correlated strongly with stomach cancer mortality*.

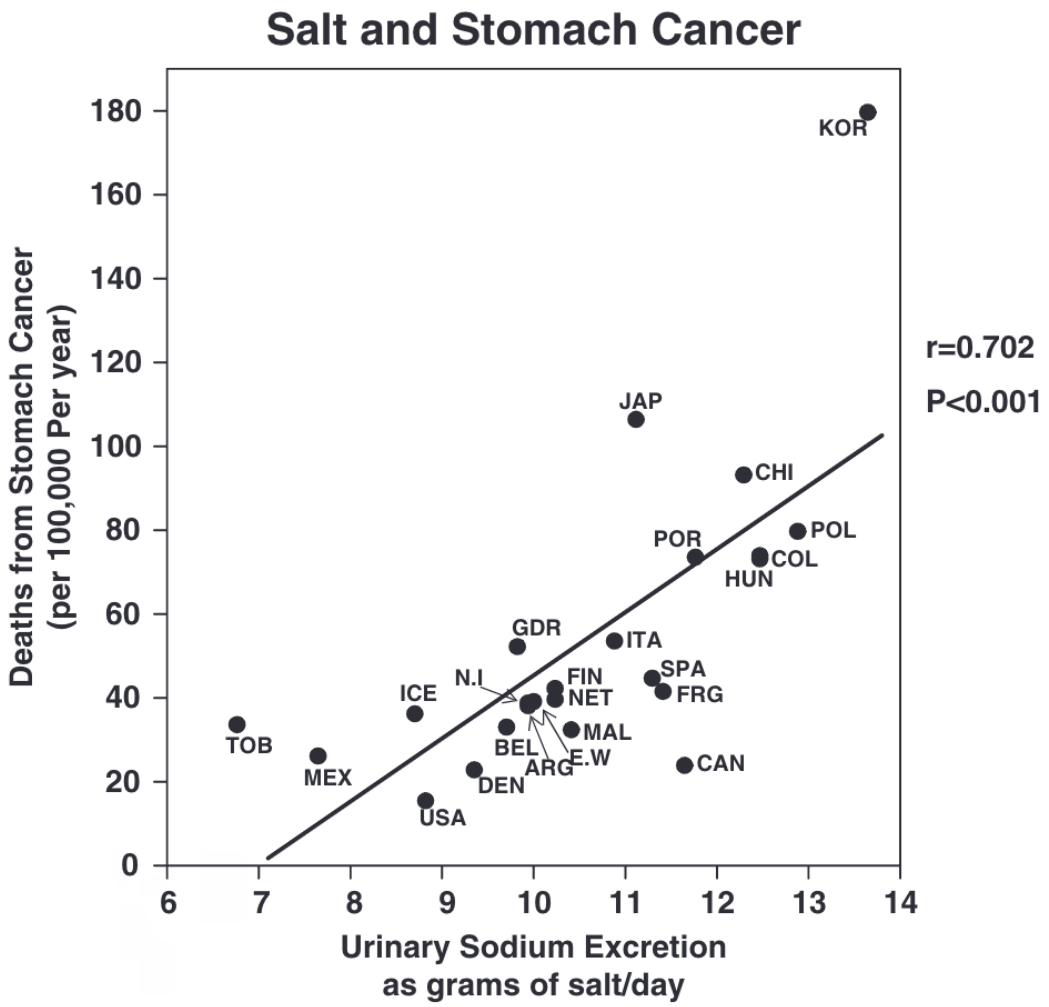


Figure *illustrating the associations between salt and gastric cancer in the INTERSALT study. The association was linear [evident by the close clustering of the data points along the solid black line] from 7g/d salt, and notable that Korea and Japan exhibited the highest mortality rates.*

This finding was not left in a historical vacuum, several studies in more recent years have demonstrated associations between salt and salt-rich foods, and risk of gastric cancer [2,3]. The present study was published in 2021 and represents the most up to date synthesis of the epidemiology of salt and gastric cancer risk.

*Geek Box: Potential Mechanisms of Sodium Influencing Gastric Cancer

A relevant question: how might sodium influence stomach cancer risk? When it comes to CVD, we know that factors like hypertension and left ventricular mass are important effects of sodium on influencing risk. But the proposed mechanisms and related experimental evidence for gastric cancer differ, as you may expect. Perhaps the mechanism which has attracted most interest to date relates to H.pylori infection, a type of bacteria which itself is one of the leading risk factors for stomach cancer. H.pylori colonises the stomach when given the opportunity to infect, and there is experimental evidence which shows that H.pylori causes more damage to epithelial cells in the stomach in the presence of high salt levels. Epidemiology of salt has also shown interactions between salt and N-nitroso compounds [often found in processed meats] on risk of stomach cancer, and mechanistic research shows that high salt levels reduce the viscous layer protecting the stomach, exposing the stomach lining to carcinogenic effects from N-nitroso compounds. There is animal evidence that sodium chloride increases expression for certain genes which may promote gastric mucosal cell proliferation, potentially resulting in chronic gastritis. Animal studies indicate that high salt intakes may result in reduced gastric blood flow, and increased inflammatory pathways, which were associated with chronic atrophic gastritis. The addition of N-nitroso carcinogenic compounds in such a high-salt gastric environment appears to rapidly generate carcinogenesis in the stomach. So overall, salt appears to act as a moderating factor to carcinogenic processes in the stomach, rather than exerting direct carcinogenic effects itself. This may be through: 1) augmenting the adverse effects of H.pylori infection; 2) reducing protection of the gastric mucosa and; 3) influencing blood flow, inflammatory, and immune pathways and promoting gastritis. In both 2) and 3), it appears that there is significant interaction with exposing the stomach to the carcinogenic effects of N-nitroso compounds.

The Study

The present study was a meta-analysis of observational research, and was conducted with the following inclusion criteria:

- **Design:** Prospective cohort design with participants free from gastric cancer at inclusion;
- **Exposures:** Total dietary salt intake, picked foods, salted fish, processed meat, and miso soup;
- **Comparison:** Lowest intake of sodium or salty food intake;
- **Outcomes:** Gastric cancer incidence and/or gastric cancer mortality.

Relevant databases were searched up to and including September 2021. The analysis compared both “high” and “moderate” levels of total sodium or specific foods to the “lowest” level.

Results: 26 studies were included in the final analysis, totalling 4,956,350 individual participants, 19,301 cases of gastric cancer, and 2,871 deaths from gastric cancer. Follow-up ranged from 4.4 to 24yrs. 16 studies were in Asian populations, 6 in European, and 4 in the US. The following are the significant findings; more detail on all findings can be found with the Figure, below.

- ***Total Salt Intake*:** Compared to the lowest salt intake, high total dietary salt intake was associated with a 25% [RR 1.25, 95% CI 1.10 – 1.41] higher risk of gastric cancer. Moderate total dietary salt intake was associated with a 20% [RR 1.20, 95% CI 1.04 – 1.38] higher risk of gastric cancer.

- ***High Pickled Food Intake*:** Compared to the lowest intake of pickled foods, high pickled foods intake was associated with a 28% [RR 1.28, 95% CI 1.05 – 1.57] higher risk of gastric cancer.

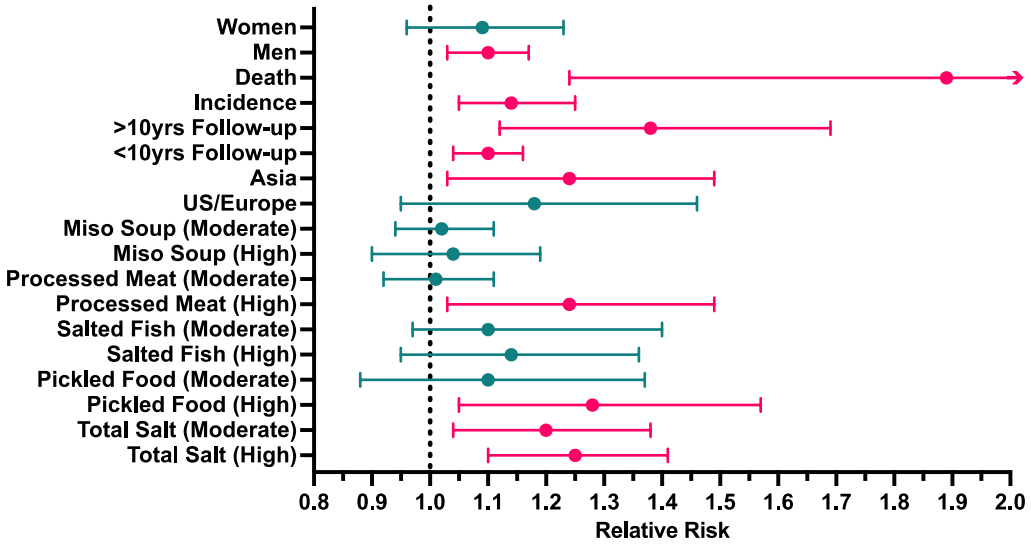
- ***High Processed Meat Intake*:** Compared to the lowest intake of processed meats, high processed meats intake was associated with a 24% [RR 1.24, 95% CI 1.03 – 1.49] higher risk of gastric cancer.

- ***Cohorts in Asia*:** Cohorts in Asia exhibited a a 32% [RR 1.32, 95% CI 1.11 – 1.55] higher gastric cancer risk, while there was no significant association in US/European cohorts [although the direction of effect was toward increased risk, RR 1.16, 95% CI 0.96 – 1.40].

- ***Duration of Follow-up*:** Cohorts with >10yrs follow-up exhibited a 38% [RR 1.38, 95% CI 1.12 – 1.69] higher risk, while cohorts with <10yrs follow-up exhibited a 10% [RR 1.10, 95% CI 1.04 – 1.16].

- ***Sex*:** Men exhibited a 10% [RR 1.10, 95% CI 1.03 – 1.17] higher risk, while women exhibited a non-significant 9% [RR 1.09, 95% CI 0.96 – 1.23].

- ***Incidence vs. Mortality*:** When stratifying cohorts by outcome, cohorts reporting gastric cancer incidence exhibited a 14% [RR 1.34, 95% CI 1.05 – 1.25] higher risk, while cohorts reporting gastric cancer incidence exhibited an 89% [RR 1.89, 95% CI 1.24 – 2.89] higher risk.



Forest plot *of outcomes in the present study. 1.0 and the vertical dashed line is the 'null'; green bars are findings that were not statistically significant, while red bars are the significant findings outlined in text above. The circle in each bar the relative risk; the bars on either side are the lower bound [left side] and upper bound [right side] of the 95% CI. Whole-food sources of salt, which are obviously more than just the salt, i.e., fish and miso soup, showed no effect, although the overall direction of effect for salted fish was more discernible than miso soup at both high and moderate levels of intake. Picked food and processed meats both exhibited more of a dose-response, where risk was primarily evident in the highest intake category. The findings in relation to cohorts in Asian and duration of follow-up have high relative risks, but as you can see from the width of the 95% CI are imprecise findings [the duration of follow-up especially]. The most robust finding overall is for high total salt intake. The finding in relation to mortality suggests a very strong effect size, however, the 95% CI were so imprecise they didn't even fit on the graph.*

The Critical Breakdown

Pros: The study is the most up-to-date synthesis of evidence on this question, and the analysis had a very large sample size and substantial number of gastric cancer cases and deaths, which is all a 'Pro' for power to detect associations. The analysis conducted a range of subgroup analyses, including region, sex, outcome, follow-up duration, and some of the major non-dietary risk factors for gastric cancer that were adjusted for in the primary included studies, specifically BMI, alcohol, and smoking [more under ***Key Characteristic***, below]. They also conducted a sensitivity analysis by removing one study at a time to see whether any one study substantially influenced the results. The quality of the studies was assessed using the Newcastle-Ottawa Scale.

Cons: An absolute pet peeve here: they didn' t define what constituted "high", "moderate", or "low" levels of anything. Not total salt, not specific salt-rich foods. They even state in the introduction that *"...clarifying the optimal salt intake in the general population for preventing gastric cancer is particularly important..."*, then proceed to clarify *nothing*. The rage. Another important 'Con' is that the primary included studies differ substantially in terms of the quality of what was adjusted for. Major risk factors for gastric cancer include age, sex, socio-economic status, region, *H.pylori* infection, obesity, smoking, alcohol, and dietary factors like high red meat, low vegetables [white vegetables in particular] and fruit intakes. Many of the included studies did adjust for some major non-dietary risk factors [including alcohol], which is a 'Pro' of the paper, but 17/26 made no dietary adjustments at all. It is possible that individual studies are therefore either underestimating or overestimating the 'true' effect of salt, which would influence the ultimate outcome of any meta-analysis.

Key Characteristic

Leaving aside the issues in relation to adjustments in the primary included studies discussed under **Cons**, above, one of the positive characteristics of this study is the extensive subgroup analysis for important potential non-dietary risk factors. And what was encouraging in these findings was that in studies that did adjust for other non-dietary risk factors, e.g., educational status [often as a proxy for socio-economic], BMI, alcohol, smoking, and physical activity, the findings were all statistically significant for the effect of high vs. low salt intake.

And those subgroup analyses were in addition to the outcomes discussed above, e.g., geographic region and sex. Thus, although the limitations in relation to the potential for dietary factors to influence the effect sizes in the individual included studies, we can at least say that the effect of high salt intake appears to be consistent across several important non-dietary risk factors for gastric cancer.

Interesting Finding

You may have noticed the differences in relation to geographic region and sex associated with gastric cancer risk in the present study. But you may be surprised to note that in this literature, these findings are not novel. In fact, if we go right the way back to the INTERSALT study referred to under ***What We Know***, above, similar findings were observed in that study in the late 1980' s, i.e., men exhibited a higher risk for gastric cancer than women, and participants in Japan, Korea, and China exhibited higher risk compared to US and/or several European cohorts [(1)].

Other studies have shown this regional distinction. For example, a 2012 meta-analysis by Ge *et al*. [(2)] showed no significant association between high salt intake and gastric cancer in European cohorts, but 27% higher odds [Odds Ratio (OR) 1.27, 95% CI 1.22 – 1.32] in Asian cohorts. In fact, confining the analysis to cohorts in Japan only, the Japanese cohorts showed 3-fold higher odds [OR 2.61, 95% CI 2.02 – 3.38] for gastric cancer. Another 2012 meta-analysis by D' Elia *et al.* [(3)], using relative risk, also showed a near 3-fold higher risk [RR 2.35, 95% C.I. 1.46 – 3.79] in Japanese cohorts, but no significant associations in US/European cohorts.

These findings remain to be fully explained but may relate to factors like higher habitual salt intakes, specific foods/condiments [i.e., soy sauce], higher prevalence of other risk factors [*H.pylori*, smoking, alcohol].

Relevance

The emphasis on salt/sodium from a health perspective is dominated by the research focus on CVD. Indeed, I am guilty of this tunnel-vision. *Mea culpa*. The present Deepdive hopefully begins to atone for this oversight, while highlighting an important association which stretches back a long time. In fact, in Japan salt was linked to gastric cancer as early as 1959 [4]. As the present study has highlighted, the geographic differences in gastric cancer risk generally, and in relation to the exposure of high salt intake, are a consistent finding in this research [2–5].

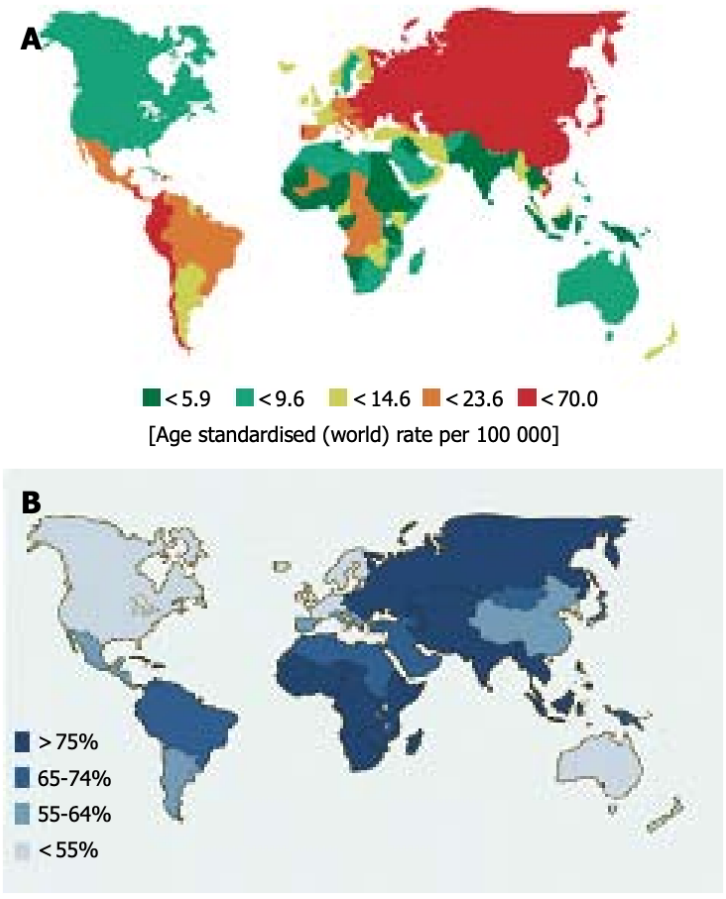


***Figure** from Crew & Neuget [5] illustrating [**top**] the prevalence of gastric cancer across the world and [**bottom**] the associated prevalence of H.pylori infection in asymptomatic adults.*

It is possible that the interaction between high sodium intakes explain, at least in part, associations of higher gastric cancer risk in Asian cohorts. For example, it has been noted that while the prevalence of *H.pylori* in both US and Japanese adults aged 20yrs is <20%, by age 40-50 the prevalence in US and Japanese adults has shifted to 40% compared to 80%, respectively. Factoring in two more risk factors – age and salt – this may mean that salt, age, and *H.pylori* all interact in the stomach to pose a higher risk of cancer.

Nevertheless, it is also important to remember that there are other potential mechanisms [as discussed in the **Geek Box**, above], and other factors may also interact – sex, duration of follow-up, and outcome – to increased risk. We will keep a tab open on this question.

Application to Practice

Put it this way: I am not sure I would bank on where I live determining the potential effect of high salt intakes on gastric cancer risk alone. Unfortunately, the major limitation of the present study is the lack of any quantification for the levels of sodium intake, and intakes of sodium-rich foods, associated with risk. This makes it difficult to compare to, for example, the recommendations for cardiovascular health, which typically are for <5-6g/d salt [<2,000-2,400mg/d sodium]. It would appear prudent to assume, in the absence of any quantification yet in relation to gastric cancer, that a similar threshold would suffice for risk reduction.

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