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REVIEW

Review of salt consumption and stomach cancer risk: Epidemiological and biological evidence

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Abstract

Stomach cancer is still the fourth most common cancer; thus, it remains an important public health burden worldwide, especially in developing countries. The remarkable geographic variations in the rates of stomach cancer indicate that dietary factors, including a range of food groups to which salt and/or nitrates have been added, may affect stomach cancer risk. In this paper, we review the results from ecologic, case-control and cohort studies on the relationship between salt or salted foods and stomach cancer risk. The majority of ecological studies indicated that the average salt intake in each population was closely correlated with gastric cancer mortality. Most case-control studies showed similar results, indicating a moderate to high increase in risk for the highest level of salt or salted food consumption. The overall results from cohort studies are not totally consistent, but are suggestive of a moderate direct association. Since salt intake has been correlated with *Helicobacter pylori* (*H pylori*) infection, it is possible that these two factors may synergize to promote the development of stomach cancer. Additionally, salt may also cause stomach cancer through directly damaging gastric mucus, improving temporary epithelial proliferation and the incidence of endogenous mutations, and inducing hypergastrinemia that leads to eventual parietal cell loss and progression to gastric cancer. Based on the considerable evidence from ecological, case-control and cohort studies worldwide and the mechanistic plausibility, limitation on salt and salted food consumption is a practical strategy for preventing gastric cancer.

Key words: Disease prevention; *Helicobacter pylori* infection; Salt consumption; Stomach cancer

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INTRODUCTION

Stomach cancer is the fourth most common cancer and is the third leading cause of cancer death worldwide[1-3]. The estimated number of stomach cancer cases worldwide was 933 900 in 2002, with two-thirds occurring in developing countries[3]. Tremendous variation in both incidence and mortality rates exists across geographic regions, with > 10-fold differences observed between low-risk and high-risk areas[4]. Although stomach cancer incidence rates have been decreasing slowly over recent decades in China, it was estimated that there were 0.4 million new cases diagnosed and 0.3 million deaths from this malignancy in 2005[5]. Therefore, this disease remains an important public health burden throughout the world, especially in developing counties including China.

Several risk factors for stomach cancer have been identified, including *Helicobacter pylori* (*H pylori*) infection, salt-preserved foods, dietary nitrite, smoking, alcohol, obesity, radiation, and family history[6,7]. Researchers also found that the incidence rates of stomach cancer varied across different geographic regions and this variation may be associated with genetic, lifestyle or environmental

factors, including diet[8]. Salt intake was first reported as a possible risk factor for stomach cancer in 1959[9]. In some early studies, using refrigerators for food storage, which may be an indicator of less salted food consumption or decreased salt intake, was found to be correlated with a reduction in stomach cancer rates[10,11], leading researchers to hypothesize that salt intake may play a role in the development of stomach cancer. A Japanese ecological study suggested a nearly linear correlation between the cumulative mortality rate of stomach cancer and the median 24 h urine salt excretion level[12,13]. Experimental studies[14,15], including rodent models, have also suggested that salt may play an important role in the etiology of stomach cancer. Based on the available experimental and epidemiological data, a report from World Health Organization (WHO)/Food and Agriculture Organization (FAO) Expert Consultation in 2003 concluded that "salt-preserved foods and salt probably increase the risk of stomach cancer"[16].

The purpose of this paper was to review the current literature on salt consumption and the risk of stomach cancer. We obtained the relevant papers and identified our literature search through PubMed from SCI papers. All cohort papers were selected with cohort size more than 2000; case-control papers were filtered out with case sample size around or more than 100. At the end, we summarized the evidence from epidemiological perspectives regarding salt intake and stomach cancer risk.

EPIDEMIOLOGICAL STUDIES OF SALT AND STOMACH CANCER RISK

When evaluating epidemiologic studies on the relationship between salt or salted food consumption and stomach cancer risk, it is essential to consider the diversity of salted foods. Some studies analyzed overall dietary salt intake, whereas others evaluated stomach cancer risk associated with salt intake in various categories, such as table salt or salted fish.

Ecologic studies

Several ecologic studies reported positive associations between different indicators of salt consumption and stomach cancer mortality at the population level[17-21]. In an ecologic study of 24 countries, median urinary sodium levels, ascertained on randomly selected samples from each country, were significantly correlated with stomach cancer mortality (r = 0.70 in men; 0.74 in women) (both $P < 0.001$)[17]. Another study evaluated correlations between both salt intake and 24 h urinary sodium excretion and stomach cancer mortality among men in four geographic regions of Japan, and reported a strong correlation between stomach cancer mortality and salt excretion, but not with dietary salt intake[21]. An ecologic study of stomach cancer mortality in 65 Chinese counties observed significant, yet modest, correlations for intake of salt-preserved vegetables (r = 0.26 in men and 0.36 in women)[18]. A Japanese study administered a 38-item food frequency questionnaire to a sample of 634 men and the wives of 373 of these men from five districts in Japan. The rank correlation coefficient between gastric cancer mortality and pickled vegetable consumption was 0.36[19]. In a similar study of 207 Japanese men and the wives of 165 of the men, average daily sodium consumption, estimated using a 3 d weighed food record, was correlated with stomach cancer mortality rates (partial rank r = 0.45)[20].

In summary, the majority of ecological studies indicated that the average salt intake in each population was closely correlated with gastric cancer mortality. However, employing dietary assessment methods in these studies has some limitations, such as variation of the questionnaire validity in different population, and use of the same composition table calculating salt intake in diverse dietary cultures. One validated questionnaire used by one population may not be appropriate or valid for another population; thus in population based studies, dietary estimates may not be highly accurate and the association between dietary factors and disease may be much compromised. Applying the same composition table to calculate the same food in different dietary culture may cause bias, since the same food in different areas may have different salt content. For example, the regional average salt content of miso in 39 regions of 20 prefectures across Japan ranged from 9.1% to 18.2%[22]. Furthermore, as with all ecologic studies, diet and stomach cancer were neither measured nor analyzed on the individual level. Rather, the diets of sampled individuals were used to represent entire populations or geographic regions. Thus, misclassification is an obvious concern. Furthermore, associations observed at the population level cannot be assumed to hold at the individual level, and causality cannot be inferred from this type of study.

Case-control studies

Forty two case-control studies on salt consumption in relation to stomach cancer are presented in Table 1[23-64]. Of these, twenty two studied overall salt, table salt or sodium[23-44], twelve estimated salted/dried fish and/or salted fish gut or cod roe[25,39,45-54], six investigated salted or pickled vegetables[25,32,52-55], three focused on salty snacks[41,56,57], and twelve studied salted foods in general[29,30,32,52,54,58-64].

Among the sixteen studies that estimated overall dietary salt or sodium intake, eight in Puerto Rico, Spain, Korea, Italy, Mexico, China (two) and USA have shown strong statistically significant increases in risk (OR = 1.5-5.0 for the highest intake levels)[28-31,33,34,36,43]. Seven of them reported statistically non-significant OR of 1.1 to 1.5 for consumption in the upper half of overall salt or sodium intake[24-27,32,35,44], and the remaining study reported no association[23]. Six of the studies specifically examined the use of table salt, with three studies (in Belgium, England, and Poland) reporting statistically significant increases in risk with OR = 1.6, 1.8, 6.2, respectively[38,40,42]. Two other studies each reported statistically non-significant odds ratios of 1.5 for consumption of the upper half of the table salt intake distribution[37,39]; the remaining study reported no

Table 1 Summary of 45 case-control studies that evaluated the association between salt consumption and stomach cancer risk

Author and year	No. of cases	No. of controls	Factors evaluated	Exposure levels and OR (95% CI)[1]
SALT AND SODIUM INTAKE				
Modan *et al*, 1974: Israel[23]	166	429	Salt	No association
Risch *et al*, 1985: Canada[24]	246	246	Salt	No association
You *et al*, 1988: China[25]	564	1131	Salt (per capita household)	≤ 13 kg/yr, ≤ 19 kg/yr, ≤ 20 kg/yr, > 20 kg/yr 1.0, 1.2, 1.1, 1.1 (0.8-1.4); NS
Negri *et al*, 1990: Italy[26]	526	1223	Salt	Low, intermediate, salty 1.0, 1.3, 1.2 (0.8-1.7); NS
Wu-Willians *et al*, 1990: USA[27]	137 male	137	Add salt	Rarely, often, always 1.0, 1.4, 1.2 (Na); NS
Nazario *et al*, 1993: Puerto Rico[28]	136	151	Salt	≤ 6.979 g/wk; 6.98-18.66 g/wk; 18.67-43.26 g/wk; ≥ 43.27 g/wk 1.0, 2.9, 4.5, 5.0 (2.1-12.0); $P < 0.05$
Ramón *et al*, 1993: Spain[29]	117	234	Salt	Quartiles 1 through 4 1.0, 1.2, 1.8, 2.1 (1.2-7.1); P for trend < 0.01
Lee *et al*, 1995: Korea[30]	213	213	Salt	Tertile 3 *vs* 1 3.7 (1.1-12.5); $P < 0.05$
La Vecchia c *et al*, 1997: Italy[31]	746	2053	Salt	Low, intermediate or high 1.0, 1.5 (1.0-2.2); $P < 0.05$
Ye *et al*, 1998: China[32]	272	544	Salt	0.25 kg/m; > 0.25 kg/m 1.0, 1.3 (1.0-1.6); NS
López-Carrillo *et al*, 1999: Mexico[33]	220	752	Salt	Never, sometimes (adding salt after tasting the food) Positive association; $P < 0.05$
Liu *et al*, 2001: China[34]	189	189	Heavy salt	Low to high half 1.0, 2.0 (1.3-3.2); $P < 0.05$
Machida-Montani *et al*, 2004: Japan[35]	122	235	Salt	Tertiles 1 through 3 1.0, 1.3, 1.5 (0.6-3.7); NS
Qiu *et al*, 2004: China[36]	103	133	Salt	Positive association; $P < 0.05$
La Vecchia *et al*, 1987: Italy[37]	206	474	Table salt	Tertile 3 *vs* 1 1.5 (Na); NS
Tuyns *et al*, 1988: Belgium[38]	293	2851	Table salt	Never, sometimes, always 1.0, 1.0, 1.8 (1.2-2.8); $P < 0.05$
Buiatti *et al*, 1989: Italy[39]	1016	1159	Table salt	Seldom, always 1.5 (1.3-1.9); NS
Coggon *et al*, 1989: England[40]	95	190	Table salt	Low to high half 1.0, 6.2 (2.0-18.9); $P < 0.05$
Boeing *et al*, 1991: Germany[41]	143	579	Table salt	No association
Boeing *et al*, 1991: Poland[42]	741	741	Table salt	Low to high half 1.0, 1.6 (1.2-2.3); $P < 0.05$
Graham *et al*, 1990: USA[43]			Sodium intake	≤ 73.2 g/mo; 73.2-98.8 g/mo; ≤ 98.9-127.3 g/mo; > 127.3 g/mo
	186 male	181		1.0, 1.8, 2.6, 3.1 (1.7-5.8); P for trend = 0.001 ≤ 66.9; 67.0-88.5; > 88.5
	107 female	104		1.0, 1.8, 4.7 (2.3-9.6); P for trend = 0.0001
Harrison *et al*, 1997: USA[44]		132	Sodium intake	Low to high half
	60 intestinal			1.0, 1.3 (0.8-1.9); NS
	31 diffuse			1.0, 1.4 (0.9-2.1); NS
SALTY FOODS				
Salted fish				
Haenszel *et al*, 1972: Japan[45]	220	440	Salted/dried fish	None, use both, 2 times/mo; 3-5 times/mo; 6 times/mo 1.0, 2.0, 1.5, 2.5, 2.6 (Na); $P < 0.05$
Haenszel *et al*, 1976: Japan[46]	783	1566	Salted/dried fish	None; < 4 times/mo; 4-9 times/mo; ≥ 10 times/mo 1.0, 1.1, 1.1, 1.2 (Na); NS
Tajima *et al*, 1985: Japan[47]	93	186	Salted/dried fish	Low to high half 1.0, 2.6 (Na); $P < 0.01$
You *et al*, 1988: China[25]	564	1131	Sated fish	≤ 0.5 kg/yr, ≤ 1 kg/yr, > 1 kg/yr 1.0, 1.0, 1.4 (0.8-1.5); NS
Buiatti *et al*, 1989: Italy[39]	1016	1159	Salted/dried fish	Tertile 3 *vs* 1 1.4 (Na); P for trend = 0.001
Kato *et al*, 1990: Japan[48]				< 2-3 times/wk; ≥ 2-3 times/wk
	289 male	1247	Salted/dried fish	1.0, 1.2 (0.9-1.7); NS
			Salted fish gut, cod roe	1.0, 1.5 (1.1-2.1); $P < 0.05$
	138 female	1767	Salted/dried fish	1.0, 0.7 (0.5-1.0); NS
			Salted fish gut, cod roe	1.0, 0.5 (0.3-1.0); NS
González *et al*, 1991: Spain[49]	354	354	Salted fish	Low to high half 1.0, 1.5 (0.9-2.6); NS
Palli *et al*, 1992: Italy[50]		1159	Salted/dried fish	Tertile 3 *vs* 1

	68 cardia 855 others			1.7 (0.9-3.1); NS 1.5 (1.2-1.8); NS
Hansson *et al*, 1993: Sweden[51]	338	669	Salted fish	None, ⩽ 0.9 times/mo; ⩽ 3 times/mo; ⩽ 7 times/mo; ⩽ 11 times/mo 1.0, 1.0, 0.9, 0.9, 1.3 (0.8-2.1); NS (adolescence) None, ⩽ 0.9 times/mo; ⩽ 3 times/mo; ⩽ 7 times/mo 1.0, 1.0, 0.8, 0.8 (0.5-1.3); NS (20 yr prior to interview)
Kim *et al*, 2002: Korea[52]	136	136	Salted fish	Tertiles 1 through 3 1.0, 0.8, 0.8 (0.4-1.6); NS
Cai *et al*, 2003: China[53]	381	222	Salty fish	< times/mo, < 3 times/wk, ⩾ 3 times/wk 1.0, 1.0, 5.5 (1.4-19.5); NS
Strumylaite *et al*, 2006: Lithuania[54]	379	1137	Salted fish	Almost do not use, 1-3 times/mo 1.0, 0.7 (0.5-0.9); *P* for trend = 0.002
Salted vegetable				
You *et al*, 1988: China[25]	564	1131	Sated vegetables	< daily, daily 1.0, 1.1 (0.7-1.8); NS
Ye *et al*, 1998: China[32]	272	544	Salted vegetables	< 2 kg/yr; > 2 kg/yr 1.0, 1.4 (1.1-1.8); *P* < 0.05
Kim *et al*, 2002: Korea[52]	136	136	Salted vegetables	Tertiles 1 through 3 1.0, 0.9, 1.5 (0.8-2.9); NS
Xibin *et al*, 2002: China[55]	210	630		Low to high half
			Pickled or salted vegetables	1.0, 4.0 (1.6-9.8); *P* < 0.05
			Preference for a high salt vegetables	1.0, 2.6 (1.6-4.3); *P* < 0.05
Cai *et al*, 2003: China[53]	381	222	Pickled vegetables	< times/M, < 3 times/w, ⩾ 3 times/wk 1.0, 1.3, 1.8 (1.0-3.0); *P* for trend = 0.038
Strumylaite *et al*, 2006: Lithuania[54]	379	1137	Pickled vegetables with salt and oil	Almost do not use, 1-3 times/mo, ⩾ 1-2 times/wk
			Pickled vegetables with salt and vinegar	1.0, 0.6, 0.8 (0.6-2.1); NS
			Salted mushrooms	Almost do not use, 1-3 times/mo, ⩾ 1-2 times/wk 1.0,0.7, 0.8 (0.6-1.0); NS 1-3 times/mo, ⩾ 1-2 times/wk 1.0, 1.6 (1.1-2.4); NS
Salted snacks				
Boeing *et al*, 1991: Germany[41]	143	579	Pretzels, salty snacks	Tertiles 1 through 3 1.0, 0.7, 1.5 (1.0-2.2); NS
Ward *et al*, 1999: Mexico[56]	220	752	Salty snacks	Never, ⩽ 2, > 2 times/mo 1.0, 1.3, 1.8 (1.2-2.8); *P* for trend = 0.008
Chen *et al*, 2002: Nebraska[57]	124	449	Salty snacks	Quartiles 1 through 4 1.0, 1.4, 1.2, 0.7 (0.3-1.6);NS
Salted foods in general				
Hu *et al*, 1988: China[58]	241	241	Salted and fermented soya paste	< 2 kg/yr; > 2 kg/yr 1.0, 1.5 (1.0-2.2); NS
Kono *et al*, 1988: Japan[59]	139	2852	Salty foods	None or 1-3 times/mo; 1-3 times/mo; once/do more 1.0, 0.8, 1.4 (Na): NS
Demirer *et al*, 1990: Turkey[60]	100	100	Salted foods	Less than once or twice/wk; once or twice/wk *vs* 1.0, 3.8 (2.1-6.9); *P* < 0.001
Hoshiyama *et al*,1992: Japan[61]	294	294 (general population) 202 (hospital control)	Salty foods	No, moderate, yes 1.0, 1.7, 2.3 (1.5-3.4); *P* < 0.01 1.0, 1.3, 1.1 (0.7-1.9); NS
Ramón *et al*, 1993: Spain[29]	117	234	Pickled foods	Quartiles 1 through 4 1.0, 1.2, 2.1, 3.7 (Na); *P* for trend < 0.01
Ji *et al*, 1998: China[62]	1124	1451	Salted foods	Occasionally, sometimes, frequently 1.0, 1.4, 1.7 (1.3-2.4); *P* for trend = 0.001
Lee *et al*, 1995: Korea[30]	213	213	Salted side dishes	Tertile 3 *vs* 1 4.5 (2.5-8.0); *P* < 0.05
Ye *et al*, 1998: China[32]	272	544	Salted fermented sea foods	< 1.5 kg/yr; > 1.5 kg/yr 1.0, 1.6 (1.2-2.0); *P* < 0.01
Kim *et al*, 2002: Korea[52]	136	136	Salty foods	Tertiles 1 through 3 1.0, 1.1, 0.9 (0.4-1.8); NS
De Stefani *et al*, 2004: Uruguay[63]	240	960	Salted meat	Tertiles 1 through 3 1.0, 1.3, 2.0 (1.4-2.9); *P* for trend = 0.0003
Campos *et al*, 2006: Colombia[64]	368	431	Salting meals before tasting	No, yes 1.0, 3.5 (1.6-7.3); *P* for trend = 0.001
Strumylaite *et al*, 2006: Lithuania[54]	379	1137	Salted meat	Almost do not use, 1-3 times/mo, ⩾ 1-2 times/wk 1.0, 1.5, 3.0 (2.2-4.0); *P* for trend < 0.001

[1]OR, Odds ratio; CI: Confidence interval; Na: No association.

Table 2 Summary of 11 cohort studies that evaluated the association between salt consumption and stomach cancer risk

Author and yr	Size of cohort	No. of cases	Length of follow-up (yr)	Factors evaluated	Exposure levels and RR (95% CI)[1]
Salt					
Nomura *et al*, 1990: USA[65]	7990 male	150	4	Table salt/shoyu	Never-seldom, after tasting, always 1.0, 1.4, 1.0 (0.6-1.6); NS
van den Brandt *et al*, 2003: Netherlands[66]	120852	282	6.3	Dietary salt	Quintiles 1 through 5 1.0, 1.5, 1.0, 1.5, 1.2 (0.8-1.8); NS
				Table salt	Never, seldom, sometimes, often/very often 1.0, 1.1, 0.7, 0.9 (0.6-1.4); NS
Tsugane *et al*, 2004: Japan[67]			12	Salt	Quintiles 1 through 5
	18684	358			Male: 1.0, 1.7, 2.0, 2.3, 2.2 (1.5-3.4); *P* for trend < 0.001
	20381	128			Female:1.0, 0.9, 1.0, 0.6, 1.3 (0.8-2.3); NS
Shikata *et al*, 2006: Japan[68]	2476	93	14	Dietary salt	< 10.0, 10.0-12.9, 13.0-15.9, ≤ 16.0 1.0, 2.1, 1.9, 2.7 (1.4-5.2); *P* for trend = 0.01
Sjödahl *et al*, 2008: Sweden[69]	73133	313	18	Dietary salt	Low to high half 1.0, 1.0 (0.7-1.4); NS
Salty foods					
Kneller *et al*, 1991: USA[70]	17633 male	75	20	Salted fish	Never, < 1, ≥ 1 1.0, 1.0, 1.9 (1.0-3.6); NS
Galanis *et al*, 1998: USA[71]	11907	108	14.8 (average)	Dried or salted fish	None, 1 or more times/wk
				High-salt foods	1.0, 1.0 (0.6-1.7); NS None, 1-3 times/wk, 4 or more times/wk 1.0, 1.0, 1.1, (0.7-1.8); NS
Ngoan *et al*, 2002: Japan[72]	13000	116	10	Salted food	Low, median, high 1.0, 1.0, 1.4 (0.6-3.2); NS
Kim *et al*, 2004: Japan[73]		400	10	Salted food	Quartiles 1 through 4
	20300			(traditional type)	Male:1.0, 2.0, 2.5, 2.9 (1.8-4.7); *P* for trend < 0.0001
	21812				Female: 1.0, 1.7, 1.3, 2.4 (1.3-4.4); *P* for trend = 0.007
Tokui *et al*, 2005: Japan[74]	110792		12	Preference for salty food	No, a little, somewhat, much, very much
		574			Male: 1.0, 0.9, 1.1, 1.1, 1.4 (0.7-2.8); NS
		285			Female: 1.0, 1.6, 1.8, 1.5, 1.9 (0.6-5.8); NS
				Dried or salty fish	None, 1-2/mo, 1-2/wk, 3-4/wk, 1+/d
		574			Male: 1.0, 0.9, 0.9, 0.9, 1.1 (0.7-1.8); NS
		285			Female:1.0, 0.6, 0.7, 0.7, 0.9 (0.5-1.6); NS
Kurosawa *et al*, 2006: Japan[75]	8035	76	11	Salted food	Low, intermediate, high 1.0, 4.0, 5.4 (1.8-16.3); *P* for trend < 0.01

[1]RR: Relative risk.

association[41].

Of the twelve studies that estimated salted fish intake, four found strong statistically significant increases in risk (OR = 1.4-5.5 for the highest intake levels)[39,45,47,48]. One Japanese study reported a statistically significant increase in risk for high consumption of salted fish gut and cod roe in males, but not females, and no significant association for salted/dried fish for both genders[48]. Seven other studies reported statistically non-significant correlations[25,46,49-53]; the remaining study reported a statistically significant inverse association with odds ratios of 0.7 for consumption in the upper half of the salted fish intake distribution[54].

Six studies in Table 1 examined salted vegetables; of these, three reported statistically significant increases in risk with higher intakes of salted vegetables[32,53,55], the remaining three studies in China, Korea and Lithuania showed no relationship to stomach cancer risk[25,52,54]. Additionally, three studies reported on salted snacks. Of them, only one study in Mexico reported a statistically significant relationship to stomach cancer[56], with the other two reporting no substantial associations[41,57].

Twelve studies examined consumption of salted soya paste, salted side dishes and salty foods in general[29,30,32,52,54,58-64]. Nine of them observed a moderate increase in risk with higher consumption (OR = 1.6-4.5)[29,30,32,54,60-64], the remaining three reported no association[52,58,59].

In summary, many case-control studies found similar results, indicating a moderate to high increase in risk for the highest level of salt or salted food consumption. Given the large number of studies that reported data on salt, sodium and salty foods consumption, some inconsistent results were to be expected. The inconsistencies may be due, at least in part, to the retrospective assessment of salt exposure, which might have changed after the diagnosis of stomach cancer. Furthermore, the degree to which each of these measures reflects total salt intake varies, and it is therefore not surprising that results would vary.

Cohort studies

Eleven cohort studies, investigating salt or salted food consumption and stomach cancer risk in the US, Japan, Sweden, and the Netherlands have produced inconsistent results (Table 2)[65-75]. When viewed separately in the Table, the results were inconsistent for both salt intake and intake of salty foods. Four Japanese studies reported

statistically significant associations (range of RR = 2.2-5.4 for the highest intake level)[67,68,73,75], including one study that reported significantly elevated risks in both men and women after 10 years follow up of 20 300 men and 21 812 women[73]. Another study, conducted in rural Japan with 8035 subjects and 76 stomach cancer deaths, reported a significantly elevated relative risk for the most frequent intake of highly salted foods compared with the least frequent intake (RR = 5.4; 1.8-16.3; *P* for trend < 0.01)[75]. In a study that examined 18 684 men and 20 381 women and included 486 histologically confirmed stomach cancer cases (358 men and 128 women), there was a dose-dependent association between salt consumption and stomach cancer risk in men (*P* for trend < 0.001), but not in women (*P* for trend = 0.48)[67]. Shikata *et al*[68] categorized 2476 subjects into four groups according to daily salt intake. After 14 years of follow-up, the age- and sex-adjusted incidence was significantly higher in the second to fourth groups than in the first group (RR = 2.4, 95% CI: 1.2-4.7; RR = 2.1, 95% CI: 1.0-4.3; RR = 3.0, 95% CI: 1.5-5.8, respectively). With the exception of these positive findings, the remaining seven cohort studies showed no substantial associations[65,66,69-72,74]. It is perhaps noteworthy that four studies with statistically significant positive results were conducted in Japan, which may be related to a potentially higher range of salt intake in that country.

In summary, some cohort studies suggest that a higher intake of salt or of salted food, as estimated by validated food frequency questionnaires, may be directly associated (or at least indirectly linked) with subsequent development of stomach cancer. Although the overall results from cohort studies are not totally consistent, they are suggestive of a moderate direct association.

EVIDENCE ON INTERACTIONS BETWEEN SALT OR SALTED FOODS AND HELICOBACTER PYLORI INFECTION

Even though *H pylori* infection is the strongest risk factor for stomach cancer, it cannot completely explain the worldwide distribution of this disease. It is very important to evaluate the potential joint effects of *H pylori* infection and other factors, including salt intake, in stomach cancer carcinogenesis.

Few epidemiological studies have investigated *H pylori* infection in relation to salt consumption. In an international ecologic study[76], statistically significant correlations between national *H pylori* infection rates and national salt excretion levels were found in older (age 50-64) men and women (r = 0.73 and r = 0.83, respectively) and in younger (age 20-34) men (r = 0.73), but not in younger women (r = 0.52). A cross-sectional study of 634 Japanese men[77] reported that daily consumption of miso soup was associated with the prevalence of *H pylori* (OR = 1.60, *P*< 0.05). Similarly, increasing consumption of pickled vegetables was associated with increased *H pylori* infection risk (OR = 1.90 for the highest level, *P* for trend = 0.02). Despite limitations inherent in these types of studies, they can nevertheless provide information on potential associations between salted foods and *H pylori* infection in humans, which may be evaluated more fully in case-control and cohort studies.

Three previous epidemiological studies have examined the potential synergistic relationship between salt consumption and *H pylori* infection in the development of stomach cancer; however, the results are inconsistent[35,68,78]. A case-control study in Japan analyzing the independent and joint effects of diet and *H pylori* infection found that subjects with *H pylori* infection and with high salt intake (OR = 14.2) had a higher odds ratio compared with subjects with *H pylori* infection and low salt intake (OR = 9.7) (reference group was no *H pylori* infection and low salt intake), but there was not a statistically significant interaction between the two risk factors[35]. A Korean case-control study investigating the role of salt and *H pylori* infection in stomach cancer found that subjects with *H pylori* infection and high salt consumption had a 10-fold risk of early stomach cancer compared with subjects without *H pylori* infection and with a low salt consumption (*P* = 0.047)[78]. These two case-control studies have some limitations, including issues of possible recall bias and misclassification. For example, both *H pylori* and salt intake were assessed after the development of stomach cancer. Advancing stomach cancer can combine with the loss of infection characterized by a fall in circulating anti-*H pylori* antibodies and changes in salt exposure (or in recollection of dietary exposures prior to the onset of disease). Only one cohort study, conducted in Japan, evaluated the potential interaction between diet and *H pylori,* and found that the positive association between increased salt intake and gastric cancer was statistically significant among subjects with *H pylori* infection only[68]. The relative risks were similar, however, and the authors note that findings for dietary salt were most pronounced in subjects who had both *H pylori* infection and atrophic gastritis. The three studies discussed above have relatively small sample sizes, ranging from 69 to 122 stomach cancer cases, and thus the estimation of relative risk is imprecise and results should be interpreted cautiously, especially in the analyses of effect modification (interaction). Finally, the tendency of case-control studies to show stronger associations than cohort studies suggests the possibility that some degree of recall bias and/or selection bias may have influenced the results of the former.

Critical issues in interpreting salt consumption with stomach cancer risk

Most epidemiological data suggest an association between salt intake and the development of stomach cancer. When interpreting these data, several issues must be considered.

Assessment of salt intake is difficult and prone to some potential biases. Many commonly used dietary assessment methods, such as food frequency questionnaires and diet records, have reported only

moderate reproducibility in epidemiological studies, and thus some misclassification of dietary intake is inevitable[79,80]. This may be particularly true of total salt intake, given its nearly ubiquitous addition to most processed foods. In addition, use of different salt assessment methods may lead to different conclusions. For example, both 24 h urinary excretion and 3 d dietary record methods for salt intake estimation were used in one Japanese ecologic study. Only urinary salt excretion level showed a strong correlation with stomach cancer mortality, while dietary salt was weakly and non-significantly correlated[21]. Although 24 h urine collection may be an optimal method in estimating routine salt intake, it is impracticable for a large-scale population study, especially a cohort study with long-term follow-up.

Another critical issue in interpreting salt consumption in relation to stomach cancer risk is the variation in the salt consumption levels across the population. To date, there is no standard method for salt intake categorization, and several studies have reasonably compared categories, such as quintiles for the application in the specific study population. Because average salt intake varies across different populations, salt consumption levels considered "high" in one study might be considered "low" in another study. For example, in a study conducted in Japan, subjects reporting once per week consumption of salted food were in the lowest exposure category[48]; in contrast, the subjects in a Turkish study reporting once per week were classified into the highest exposure level (defined as $\geqslant$1-2 times/week)[60]. Finally, in some studies[75], salted food levels were calculated from the sum of the scores of foods belonging to the food items (pickled vegetable + foods deep-boiled in soy sauce), making it impossible to compare effects at similar levels of consumption across studies.

Because of the complexity of diets, the traditional approach with a single nutrient may potentially be confounded by the interactions between food components that are likely to be interactive or synergistic[81]. It is possible that the increased risks in stomach cancer could be due to compounds other than salt in foods that were produced during the preservation process[56]. In East Asia, salted foods and sauces are also high in NO_3, a chemical carcinogen, which may either be added to the foods or synergize from amino acids during fermentation. Nitrite and salt may work at an early stage[82] in a synergistic fashion on stomach cancer carcinogenesis[17] that might cause the strong associations between highly salted foods and gastric cancer[67]. However, nitrite was not clearly related with stomach cancer risk[83] and its function may be influenced by other factors. For example, when lower salt intake was combined with higher NO_3 intake, stomach cancer mortality rates tended to be lower[17]. However, this might be explained by a higher intake of fresh fruits and vegetables, which are the major source of nitrate and also protect against cancer[84,85].

Moreover, it may be difficult to separate the effects of salt from other nutrients that may contribute to stomach cancer risk. The absence of adjustment for confounding factors (such as age, sex, smoking and dietary habit) can hamper the statistical estimation causing over- or underestimation of the real association between salt or salted food and stomach cancer. In Tables 1 and 2, few studies have controlled for dietary factors in their analyses of salt consumption, which makes it difficult to compare the different studies according to the dietary variables adjusted in the analysis. However, the study results that were adjusted by a wide range of potentially confounding variables, such as age, sex, *H pylori* infection, atrophic gastritis, medical history of peptic ulcer, family history of cancer, body mass index, diabetes, total cholesterol, physical activity, alcohol intake, smoking habit and other dietary factors[68], showed no difference from the crude results. Studies with adjustment for some or most of the above potential confounding factors[66,68,72,73] showed no systematically apparent differences from the studies with adjustment for a few or several confounders.

BIOLOGICAL MECHANISMS

Several mechanisms by which salt intake may increase stomach cancer risk have been postulated, although to date there has been no consistent conclusion. High dietary salt intake may potentiate the colonization of *H pylori*[86], a known risk factor for stomach cancer, through the increase of surface mucous cell mucin and decrease of gland mucous cell mucin[87]. At the molecular level, high dietary salt intake may potentiate *CagA* (*H pylori* gene) expression and enhance the ability of *CagA* to translocate into gastric epithelial cells and enhance the ability of *H pylori* to alter gastric epithelial cell function[15]. Another explanation for the potential effect of high salt intake in gastric carcinogenesis is that high dietary salt intake helps to change the mucous viscosity protecting the stomach, potentiate exposure to carcinogens such as N-nitroso compounds, and lead to cell death[88]. In addition, high salt intake can cause damage to, and inflammatory responses of, the gastric epithelium[14], which may increase epithelial cell proliferation as part of the repair process and increase the probability of endogenous mutations[89,90]. One mechanism of high salt action in gastric carcinogenesis has been considered to induce hypergastrinemia in *H pylori*-infected gerbils[87]. Gastrin itself may mediate epithelial cell growth in *H pylori*-colonized mucosa[91] and chronic hypergastrinemia can synergize with *Helicobacter* infection and lead to eventual parietal cell loss and progression to gastric cancer[92].

ANIMAL STUDIES OF SALT AND STOMACH CANCER

Most published animal studies focus on the relationship between gastric cancer and several important suspected carcinogens, salt, *H pylori*, N-methyl-N-nitro-N-nitrosoguanidine (MNNG), and 4-nitroquinoline-1-oxide (NQO). In general, salt alone has no apparent

effect on the development of gastric carcinogenesis, but administration of salt in rats induced a concentration-dependent damage of surface mucous cell layer, and also increased replicative DNA synthesis[89]. Interestingly, a synergistic effect was observed when salt and other risk factors (*H pylori*, MNNG, NQO) were analyzed simultaneously. This conclusion was derived in animal experiments addressing gastric carcinogenesis from both the molecular level and tumor progression. At the molecular level, a high salt diet was associated with an elevation of anti-*H pylori* antibody titers, serum gastrin levels, and inflammatory cell infiltration in a dose dependent model in Mongolian gerbils infected with *H pylori*[87]. Similarly, in *H pylori* infected gerbils, a high-salt diet significantly up-regulated the expression of cyclooxygenase-2 (COX-2), and nitric oxide synthase (iNOS)[93]; the number of colony-forming units was also significantly higher. Dietary sodium chloride also produced a reduction in cell yield, and an increase in S-phase cell numbers that are the most susceptible to mutagenesis, which may possibly increase tumor incidence[90]. Several studies examined gastric tumor progression in mice infected with *H pylori* and administered with a high-salt diet, and all of these studies consistently demonstrate that a high-salt diet enhances the effects of *H pylori* infection, and consequently promotes the development of stomach cancers[88,94,95]. Additionally, a high-salt diet significantly increased gastric tumor incidence in those mice pre-treated with MNNG[14] or MNU[96], suggesting that salt and chemical carcinogens also exert a synergistic effect in the development of gastric carcinogenesis.

CONCLUSION

Most published epidemiological studies provide positive evidence for an association between salt or salted food consumption and stomach cancer risk, which was also supported by experimental studies[14,87,94,97]. The limitations of salt assessment in epidemiological studies may have attenuated the true effect of salt intake on stomach cancer risk, or even biased the results away from the null, in the reviewed ecological, case-control, and cohort studies. Ideally, dietary modification of salt intake, as well as eradication of *H pylori* infection, is a promising strategy for gastric cancer prevention throughout the world, especially in developing counties. However, the former strategy is more practical than the latter according to previous epidemiological studies. Future studies that address the association with salt and other dietary factors and the interactions between these factors in different aspects, e.g. molecular level, may help to shed light on the etiology of stomach cancer.

REFERENCES

1 **Kamangar F**, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006; **24**: 2137-2150

2 **Stewart BW**, Kleihues P. World Cancer Report. Lyon: IARC Press, 2003

3 **Parkin DM**. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006; **118**: 3030-3044

4 **Parkin DM**. International variation. *Oncogene* 2004; **23**: 6329-6340

5 **Yang L**, Parkin DM, Ferlay J, Li L, Chen Y. Estimates of cancer incidence in China for 2000 and projections for 2005. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 243-250

6 **Crew KD**, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006; **12**: 354-362

7 **Forman D**, Burley VJ. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. *Best Pract Res Clin Gastroenterol* 2006; **20**: 633-649

8 **Armstrong B**, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* 1975; **15**: 617-631

9 **Sato T**, Fukuyama T, Suzuki T, Takayanagi J, Murakami T, Shiotsuki N, Tanaka R, Tsuji R. Studies of causation of gastric cancer 2. The relation between gastric cancer mortality rate and salted food intake in several places in Japan. *Bull Inst Public Health* 1959; **8**: 187-198

10 **Boeing H**, Frentzel-Beyme R. Regional risk factors for stomach cancer in the FRG. *Environ Health Perspect* 1991; **94**: 83-89

11 **La Vecchia C**, Negri E, D'Avanzo B, Franceschi S. Electric refrigerator use and gastric cancer risk. *Br J Cancer* 1990; **62**: 136-137

12 **Tsugane S**, Gey F, Ichinowatari Y, Miyajima Y, Ishibashi T, Matsushima S, Hirota Y, Inami T, Yamaguchi M, Karita K. Cross-sectional epidemiologic study for assessing cancer risks at the population level. I. Study design and participation rate. *J Epidemiol* 1992; **2**: 75-81

13 **Tsugane S**, Gey F, Ichinowatari Y, Miyajima Y, Ishibashi T, Matsushima S, Hirota Y, Inami T, Yamaguchi M, Karita K. Cross-sectional epidemiologic study for assessing cancer risks at the population level. II. Baseline data and correlation analysis. *J Epidemiol* 1992; **2**: 83-89

14 **Takahashi M**, Hasegawa R. Enhancing effects of dietary salt on both initiation and promotion stages of rat gastric carcinogenesis. *Princess Takamatsu Symp* 1985; **16**: 169-182

15 **Loh JT**, Torres VJ, Cover TL. Regulation of Helicobacter pylori cagA expression in response to salt. *Cancer Res* 2007; **67**: 4709-4715

16 **World Cancer Research Fund, American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: a Global Perspective**. Washington DC: American Institute for Cancer Research, 1997

17 **Joossens JV**, Hill MJ, Elliott P, Stamler R, Lesaffre E, Dyer A, Nichols R, Kesteloot H. Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group. *Int J Epidemiol* 1996; **25**: 494-504

18 **Kneller RW**, Guo WD, Hsing AW, Chen JS, Blot WJ, Li JY, Forman D, Fraumeni JF Jr. Risk factors for stomach cancer in sixty-five Chinese counties. *Cancer Epidemiol Biomarkers Prev* 1992; **1**: 113-118

19 **Tsubono Y**, Kobayashi M, Tsugane S. Food consumption and gastric cancer mortality in five regions of Japan. *Nutr Cancer* 1997; **27**: 60-64

20 **Tsubono Y**, Takahashi T, Iwase Y, Iitoi Y, Akabane M, Tsugane S. Nutrient consumption and gastric cancer mortality in five regions of Japan. *Nutr Cancer* 1997; **27**: 310-315

21 **Tsugane S**, Akabane M, Inami T, Matsushima S, Ishibashi T, Ichinowatari Y, Miyajima Y, Watanabe S. Urinary salt excretion and stomach cancer mortality among four Japanese populations. *Cancer Causes Control* 1991; **2**: 165-168

22 **Watanabe T**, Miyasaka M, Koizumi A, Ikeda M. Regional difference in sodium chloride content in home-made and store-bought preparations of miso paste. *Tohoku J Exp Med* 1982; **137**: 305-313

23 **Modan B**, Lubin F, Barell V, Greenberg RA, Modan M, Graham S. The role of starches in etiology of gastric cancer. *Cancer* 1974; **34**: 2087-2092
24 **Risch HA**, Jain M, Choi NW, Fodor JG, Pfeiffer CJ, Howe GR, Harrison LW, Craib KJ, Miller AB. Dietary factors and the incidence of cancer of the stomach. *Am J Epidemiol* 1985; **122**: 947-959
25 **You WC**, Blot WJ, Chang YS, Ershow AG, Yang ZT, An Q, Henderson B, Xu GW, Fraumeni JF Jr, Wang TG. Diet and high risk of stomach cancer in Shandong, China. *Cancer Res* 1988; **48**: 3518-3523
26 **Negri E**, La Vecchia C, D'Avanzo B, Gentile A, Boyle P, Franceschi S. Salt preference and the risk of gastrointestinal cancers. *Nutr Cancer* 1990; **14**: 227-232
27 **Wu-Williams AH**, Yu MC, Mack TM. Life-style, workplace, and stomach cancer by subsite in young men of Los Angeles County. *Cancer Res* 1990; **50**: 2569-2576
28 **Nazario CM**, Szklo M, Diamond E, Román-Franco A, Climent C, Suarez E, Conde JG. Salt and gastric cancer: a case-control study in Puerto Rico. *Int J Epidemiol* 1993; **22**: 790-797
29 **Ramón JM**, Serra-Majem L, Cerdó C, Oromí J. Nutrient intake and gastric cancer risk: a case-control study in Spain. *Int J Epidemiol* 1993; **22**: 983-988
30 **Lee JK**, Park BJ, Yoo KY, Ahn YO. Dietary factors and stomach cancer: a case-control study in Korea. *Int J Epidemiol* 1995; **24**: 33-41
31 **La Vecchia C**, Negri E, Franceschi S, Decarli A. Case-control study on influence of methionine, nitrite, and salt on gastric carcinogenesis in northern Italy. *Nutr Cancer* 1997; **27**: 65-68
32 **Ye W**, Yi Y, Luo R. [A case-control study on diet and gastric cancer] *Zhonghua Yu Fang Yi Xue Za Zhi* 1998; **32**: 100-102
33 **López-Carrillo L**, López-Cervantes M, Ward MH, Bravo-Alvarado J, Ramírez-Espitia A. Nutrient intake and gastric cancer in Mexico. *Int J Cancer* 1999; **83**: 601-605
34 **Liu X**, Wang Q, Ma J. [A case-control study on the risk factors of stomach cancer in Tianjin city] *Zhonghua Liu Xing Bing Xue Za Zhi* 2001; **22**: 362-364
35 **Machida-Montani A**, Sasazuki S, Inoue M, Natsukawa S, Shaura K, Koizumi Y, Kasuga Y, Hanaoka T, Tsugane S. Association of Helicobacter pylori infection and environmental factors in non-cardia gastric cancer in Japan. *Gastric Cancer* 2004; **7**: 46-53
36 **Qiu JL**, Chen K, Wang XB, Wang JY, Zhang LJ, Shui LM. [A case-control study on the relationship between nutrition and gastric cancer in islanders] *Zhonghua Liu Xing Bing Xue Za Zhi* 2004; **25**: 487-491
37 **La Vecchia C**, Negri E, Decarli A, D'Avanzo B, Franceschi S. A case-control study of diet and gastric cancer in northern Italy. *Int J Cancer* 1987; **40**: 484-489
38 **Tuyns AJ**. Salt and gastrointestinal cancer. *Nutr Cancer* 1988; **11**: 229-232
39 **Buiatti E**, Palli D, Decarli A, Amadori D, Avellini C, Bianchi S, Biserni R, Cipriani F, Cocco P, Giacosa A. A case-control study of gastric cancer and diet in Italy. *Int J Cancer* 1989; **44**: 611-616
40 **Coggon D**, Barker DJ, Cole RB, Nelson M. Stomach cancer and food storage. *J Natl Cancer Inst* 1989; **81**: 1178-1182
41 **Boeing H**, Frentzel-Beyme R, Berger M, Berndt V, Göres W, Körner M, Lohmeier R, Menarcher A, Männl HF, Meinhardt M. Case-control study on stomach cancer in Germany. *Int J Cancer* 1991; **47**: 858-864
42 **Boeing H**, Jedrychowski W, Wahrendorf J, Popiela T, Tobiasz-Adamczyk B, Kulig A. Dietary risk factors in intestinal and diffuse types of stomach cancer: a multicenter case-control study in Poland. *Cancer Causes Control* 1991; **2**: 227-233
43 **Graham S**, Haughey B, Marshall J, Brasure J, Zielezny M, Freudenheim J, West D, Nolan J, Wilkinson G. Diet in the epidemiology of gastric cancer. *Nutr Cancer* 1990; **13**: 19-34
44 **Harrison LE**, Zhang ZF, Karpeh MS, Sun M, Kurtz RC. The role of dietary factors in the intestinal and diffuse histologic subtypes of gastric adenocarcinoma: a case-control study in the U.S. *Cancer* 1997; **80**: 1021-1028
45 **Haenszel W**, Kurihara M, Segi M, Lee RK. Stomach cancer among Japanese in Hawaii. *J Natl Cancer Inst* 1972; **49**: 969-988
46 **Haenszel W**, Kurihara M, Locke FB, Shimuzu K, Segi M. Stomach cancer in Japan. *J Natl Cancer Inst* 1976; **56**: 265-274
47 **Tajima K**, Tominaga S. Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. *Jpn J Cancer Res* 1985; **76**: 705-716
48 **Kato I**, Tominaga S, Ito Y, Kobayashi S, Yoshii Y, Matsuura A, Kameya A, Kano T. A comparative case-control analysis of stomach cancer and atrophic gastritis. *Cancer Res* 1990; **50**: 6559-6564
49 **González CA**, Sanz JM, Marcos G, Pita S, Brullet E, Saigi E, Badia A, Riboli E. Dietary factors and stomach cancer in Spain: a multi-centre case-control study. *Int J Cancer* 1991; **49**: 513-519
50 **Palli D**, Bianchi S, Decarli A, Cipriani F, Avellini C, Cocco P, Falcini F, Puntoni R, Russo A, Vindigni C. A case-control study of cancers of the gastric cardia in Italy. *Br J Cancer* 1992; **65**: 263-266
51 **Hansson LE**, Nyrén O, Bergström R, Wolk A, Lindgren A, Baron J, Adami HO. Diet and risk of gastric cancer. A population-based case-control study in Sweden. *Int J Cancer* 1993; **55**: 181-189
52 **Kim HJ**, Chang WK, Kim MK, Lee SS, Choi BY. Dietary factors and gastric cancer in Korea: a case-control study. *Int J Cancer* 2002; **97**: 531-535
53 **Cai L**, Zheng ZL, Zhang ZF. Risk factors for the gastric cardia cancer: a case-control study in Fujian Province. *World J Gastroenterol* 2003; **9**: 214-218
54 **Strumylaite L**, Zickute J, Dudzevicius J, Dregval L. Salt-preserved foods and risk of gastric cancer. *Medicina* (Kaunas) 2006; **42**: 164-170
55 **Xibin S**, Moller H, Evans HS, Dixing D, Wenjie D, Jianbang L. Residential Environment, Diet and Risk of Stomach Cancer: a Case-control Study in Linzhou, China. *Asian Pac J Cancer Prev* 2002; **3**: 167-172
56 **Ward MH**, López-Carrillo L. Dietary factors and the risk of gastric cancer in Mexico City. *Am J Epidemiol* 1999; **149**: 925-932
57 **Chen H**, Ward MH, Graubard BI, Heineman EF, Markin RM, Potischman NA, Russell RM, Weisenburger DD, Tucker KL. Dietary patterns and adenocarcinoma of the esophagus and distal stomach. *Am J Clin Nutr* 2002; **75**: 137-144
58 **Hu JF**, Zhang SF, Jia EM, Wang QQ, Liu SD, Liu YY, Wu YP, Cheng YT. Diet and cancer of the stomach: a case-control study in China. *Int J Cancer* 1988; **41**: 331-335
59 **Kono S**, Ikeda M, Tokudome S, Kuratsune M. A case-control study of gastric cancer and diet in northern Kyushu, Japan. *Jpn J Cancer Res* 1988; **79**: 1067-1074
60 **Demirer T**, Icli F, Uzunalimoglu O, Kucuk O. Diet and stomach cancer incidence. A case-control study in Turkey. *Cancer* 1990; **65**: 2344-2348
61 **Hoshiyama Y**, Sasaba T. A case-control study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption in Saitama Prefecture, Japan. *Cancer Causes Control* 1992; **3**: 441-448
62 **Ji BT**, Chow WH, Yang G, McLaughlin JK, Zheng W, Shu XO, Jin F, Gao RN, Gao YT, Fraumeni JF Jr. Dietary habits and stomach cancer in Shanghai, China. *Int J Cancer* 1998; **76**: 659-664
63 **De Stefani E**, Correa P, Boffetta P, Deneo-Pellegrini H, Ronco AL, Mendilaharsu M. Dietary patterns and risk of gastric cancer: a case-control study in Uruguay. *Gastric Cancer* 2004; **7**: 211-220
64 **Campos FI**, Koriyama C, Akiba S, Carrasquilla G, Serra M, Carrascal E, Itoh T, Minakami Y, Eizuru Y. Environmental factors related to gastric cancer associated with Epstein-Barr virus in Colombia. *Asian Pac J Cancer Prev* 2006; **7**: 633-637
65 **Nomura A**, Grove JS, Stemmermann GN, Severson RK. A

prospective study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption. *Cancer Res* 1990; **50**: 627-631
66 **van den Brandt PA**, Botterweck AA, Goldbohm RA. Salt intake, cured meat consumption, refrigerator use and stomach cancer incidence: a prospective cohort study (Netherlands). *Cancer Causes Control* 2003; **14**: 427-438
67 **Tsugane S**, Sasazuki S, Kobayashi M, Sasaki S. Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. *Br J Cancer* 2004; **90**: 128-134
68 **Shikata K**, Kiyohara Y, Kubo M, Yonemoto K, Ninomiya T, Shirota T, Tanizaki Y, Doi Y, Tanaka K, Oishi Y, Matsumoto T, Iida M. A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. *Int J Cancer* 2006; **119**: 196-201
69 **Sjödahl K**, Jia C, Vatten L, Nilsen T, Hveem K, Lagergren J. Salt and gastric adenocarcinoma: a population-based cohort study in Norway. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 1997-2001
70 **Kneller RW**, McLaughlin JK, Bjelke E, Schuman LM, Blot WJ, Wacholder S, Gridley G, CoChien HT, Fraumeni JF Jr. A cohort study of stomach cancer in a high-risk American population. *Cancer* 1991; **68**: 672-678
71 **Galanis DJ**, Kolonel LN, Lee J, Nomura A. Intakes of selected foods and beverages and the incidence of gastric cancer among the Japanese residents of Hawaii: a prospective study. *Int J Epidemiol* 1998; **27**: 173-180
72 **Ngoan LT**, Mizoue T, Fujino Y, Tokui N, Yoshimura T. Dietary factors and stomach cancer mortality. *Br J Cancer* 2002; **87**: 37-42
73 **Kim MK**, Sasaki S, Sasazuki S, Tsugane S. Prospective study of three major dietary patterns and risk of gastric cancer in Japan. *Int J Cancer* 2004; **110**: 435-442
74 **Tokui N**, Yoshimura T, Fujino Y, Mizoue T, Hoshiyama Y, Yatsuya H, Sakata K, Kondo T, Kikuchi S, Toyoshima H, Hayakawa N, Kubo T, Tamakoshi A. Dietary habits and stomach cancer risk in the JACC Study. *J Epidemiol* 2005; **15** Suppl 2: S98-108
75 **Kurosawa M**, Kikuchi S, Xu J, Inaba Y. Highly salted food and mountain herbs elevate the risk for stomach cancer death in a rural area of Japan. *J Gastroenterol Hepatol* 2006; **21**: 1681-1686
76 **Beevers DG**, Lip GY, Blann AD. Salt intake and Helicobacter pylori infection. *J Hypertens* 2004; **22**: 1475-1477
77 **Tsugane S**, Tei Y, Takahashi T, Watanabe S, Sugano K. Salty food intake and risk of Helicobacter pylori infection. *Jpn J Cancer Res* 1994; **85**: 474-478
78 **Lee SA**, Kang D, Shim KN, Choe JW, Hong WS, Choi H. Effect of diet and Helicobacter pylori infection to the risk of early gastric cancer. *J Epidemiol* 2003; **13**: 162-168
79 **Kroke A**, Klipstein-Grobusch K, Voss S, Möseneder J, Thielecke F, Noack R, Boeing H. Validation of a self-administered food-frequency questionnaire administered in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study: comparison of energy, protein, and macronutrient intakes estimated with the doubly labeled water, urinary nitrogen, and repeated 24-h dietary recall methods. *Am J Clin Nutr* 1999; **70**: 439-447
80 **Willett W**, Nutritional Epidemiology, Walter Willett. 2nd edition, Oxford: Oxford University Press, 1998
81 **Hu FB**. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol* 2002; **13**: 3-9
82 **Correa P**, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for gastric cancer epidemiology. *Lancet* 1975; **2**: 58-60
83 **van Loon AJ**, Botterweck AA, Goldbohm RA, Brants HA, van Klaveren JD, van den Brandt PA. Intake of nitrate and nitrite and the risk of gastric cancer: a prospective cohort study. *Br J Cancer* 1998; **78**: 129-135
84 **Correa P**. Diet modification and gastric cancer prevention. *J Natl Cancer Inst Monogr* 1992; 75-78
85 **Weisburger JH**. Causes of gastric and esophageal cancer. Possible approach to prevention by vitamin C. *Int J Vitam Nutr Res Suppl* 1985; **27**: 381-402
86 **Fox JG**, Dangler CA, Taylor NS, King A, Koh TJ, Wang TC. High-salt diet induces gastric epithelial hyperplasia and parietal cell loss, and enhances Helicobacter pylori colonization in C57BL/6 mice. *Cancer Res* 1999; **59**: 4823-4828
87 **Kato S**, Tsukamoto T, Mizoshita T, Tanaka H, Kumagai T, Ota H, Katsuyama T, Asaka M, Tatematsu M. High salt diets dose-dependently promote gastric chemical carcinogenesis in Helicobacter pylori-infected Mongolian gerbils associated with a shift in mucin production from glandular to surface mucous cells. *Int J Cancer* 2006; **119**: 1558-1566
88 **Tatematsu M**, Takahashi M, Fukushima S, Hananouchi M, Shirai T. Effects in rats of sodium chloride on experimental gastric cancers induced by N-methyl-N-nitro-N-nitrosoguanidine or 4-nitroquinoline-1-oxide. *J Natl Cancer Inst* 1975; **55**: 101-106
89 **Furihata C**, Ohta H, Katsuyama T. Cause and effect between concentration-dependent tissue damage and temporary cell proliferation in rat stomach mucosa by NaCl, a stomach tumor promoter. *Carcinogenesis* 1996; **17**: 401-406
90 **Charnley G**, Tannenbaum SR. Flow cytometric analysis of the effect of sodium chloride on gastric cancer risk in the rat. *Cancer Res* 1985; **45**: 5608-5616
91 **Peek RM Jr**, Wirth HP, Moss SF, Yang M, Abdalla AM, Tham KT, Zhang T, Tang LH, Modlin IM, Blaser MJ. Helicobacter pylori alters gastric epithelial cell cycle events and gastrin secretion in Mongolian gerbils. *Gastroenterology* 2000; **118**: 48-59
92 **Wang TC**, Dangler CA, Chen D, Goldenring JR, Koh T, Raychowdhury R, Coffey RJ, Ito S, Varro A, Dockray GJ, Fox JG. Synergistic interaction between hypergastrinemia and Helicobacter infection in a mouse model of gastric cancer. *Gastroenterology* 2000; **118**: 36-47
93 **Toyoda T**, Tsukamoto T, Hirano N, Mizoshita T, Kato S, Takasu S, Ban H, Tatematsu M. Synergistic upregulation of inducible nitric oxide synthase and cyclooxygenase-2 in gastric mucosa of Mongolian gerbils by a high-salt diet and Helicobacter pylori infection. *Histol Histopathol* 2008; **23**: 593-599
94 **Nozaki K**, Shimizu N, Inada K, Tsukamoto T, Inoue M, Kumagai T, Sugiyama A, Mizoshita T, Kaminishi M, Tatematsu M. Synergistic promoting effects of Helicobacter pylori infection and high-salt diet on gastric carcinogenesis in Mongolian gerbils. *Jpn J Cancer Res* 2002; **93**: 1083-1089
95 **Nozaki K**, Tsukamoto T, Tatematsu M. [Effect of high salt diet and Helicobacter pylori infection on gastric carcinogenesis] *Nippon Rinsho* 2003; **61**: 36-40
96 **Leung WK**, Wu KC, Wong CY, Cheng AS, Ching AK, Chan AW, Chong WW, Go MY, Yu J, To KF, Wang X, Chui YL, Fan DM, Sung JJ. Transgenic cyclooxygenase-2 expression and high salt enhanced susceptibility to chemical-induced gastric cancer development in mice. *Carcinogenesis* 2008; **29**: 1648-1654
97 **Shimizu N**, Kaminishi M, Tatematsu M, Tsuji E, Yoshikawa A, Yamaguchi H, Aoki F, Oohara T. Helicobacter pylori promotes development of pepsinogen-altered pyloric glands, a preneoplastic lesion of glandular stomach of BALB/c mice pretreated with N-methyl-N-nitrosourea. *Cancer Lett* 1998; **123**: 63-69

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