Dietary Salt Intake and Risk of Gastric Cancer

Lanfranco D'Elia, Ferruccio Galletti and Pasquale Strazzullo

Abstract

Humans began to use large amounts of salt for the main purpose of food preservation approximately 5,000 years ago and, although since then advanced technologies have been developed allowing drastic reduction in the use of salt for food storage, excess dietary salt intake remains very common. Gastric cancer is a common neoplasia, and dietary factors, including salt consumption, are considered relevant to its causation. A number of experimental studies supported the cocarcinogenic effect of salt through synergic action with Helicobacter pylori infection, in addition to some independent effects such as increase in the rate of cell proliferation and of endogenous mutations. Many epidemiological studies analyzed the relationship between excess salt intake and risk of gastric cancer. Both cross-sectional and prospective studies indicated a possibly dose-dependent positive association. In particular, a comprehensive meta-analysis of longitudinal studies detected a strong adverse effect of total salt intake and salt-rich foods on the risk of gastric cancer in the general population. Altogether, the epidemiological, clinical, and experimental evidence supports the possibility of a substantial reduction in the rates of gastric cancer through progressive reduction in population salt intake.

L. D'Elia · F. Galletti · P. Strazzullo
Department of Clinical and Experimental Medicine, "Federico II" University of Naples, Naples, Italy

P. Strazzullo (✉)
Department of Clinical and Experimental Medicine ESH—Excellence Center of Hypertension, "Federico II" University Medical School, via S. Pansini, 5, 80131, Naples, Italy
e-mail: strazzul@unina.it

V. Zappia et al. (eds.), *Advances in Nutrition and Cancer*,
Cancer Treatment and Research 159, DOI: 10.1007/978-3-642-38007-5_6,

Keywords
Salt intake · Gastric cancer · Risk · Food storage · Helicobacter pylori · Risk factor

Abbreviations

HP	*Helicobacter pylori*
COX-2	Cyclooxygenase-2
iNOS	Inducible nitric oxide synthases
CagA	Cytotoxin-associated gene A
MNNG	Methylnitronitrosoguanidine
MNU	N-nitroso-N-methylurea

Contents

1 Introduction

Sodium is the most abundant electrolyte in extracellular fluid and as such has a major role in the regulation of body fluid volume, plasma osmolality, and cell membrane potential. In the course of evolution, the human body has developed powerful mechanisms to preserve its sodium and chloride content and to maintain the sodium concentration in the extracellular fluid within a relatively narrow range [1]. Up to approximately 5,000 years ago, the sodium content in the human diet was extremely low since the salt content of natural foods is quite modest [2]. Switching to a much higher salt intake occurred as a result of the discovery that the addition of salt to many foods was useful to preserve them from rapid deterioration [3]; this high salt intake has been sustained since then despite the widespread availability of modern technologies for food preservation. The current unjustifiably large excess in dietary salt intake has meanwhile been recognized as a major worldwide hazard to community health being causally associated with epidemic disorders such as hypertension [4, 5], cardiovascular accidents [6], renal dysfunction [7], nephrolithiasis [8], and osteoporosis [9].

Gastric cancer is a common neoplasia and is the third leading cause of death from cancer worldwide [10, 11, 12]. Although there are large geographic and ethnic differences in its incidence and its overall rate has been slowly decreasing over recent decades, this disease is still an important public health burden and, at least partly, a preventable public health problem throughout the world [10, 11, 12]. Evidence has been provided for more or less strong associations between gastric cancer and a few dietary factors, among which is the dietary salt content and the habitual consumption of salt-rich foods. In this regard, many case-control studies detected an adverse effect of high salt consumption on the risk of gastric cancer WCRF [13]. Also, a number of prospective studies have been performed to investigate the relationship between salt or salted food consumption and risk of stomach cancer. A recent meta-analysis of these studies has shown that dietary salt intake is directly associated with the risk of gastric cancer, with progressively increasing risk across increasing levels of habitual consumption [14]. This epidemiological evidence is supported by the results of clinical and experimental studies which found that high salt intake may alter the viscosity of the gastric protective mucous barrier [15] and increase the colonization by *Helicobacter pylori* (HP), a recognized risk factor for gastric cancer [16]. High intra-gastric sodium concentrations were shown to cause mucosal damage and inflammation, which in turn has been reported to increase cell proliferation and endogenous mutations [17, 18].

This chapter will focus mainly on recent epidemiological advances concerning the association between excess salt intake and risk of gastric cancer and will also touch on the possible mechanisms whereby excess salt may promote the development of gastric cancer.

2 Salt Intake and Gastric Cancer: Epidemiological Evidence

Incidence rates of gastric cancer are different among geographic regions, and this variability may be due to lifestyle and/or environmental factors in addition to genetic susceptibility. Migration studies have focused on the association between salt and gastric cancer. Analyses of Japanese migrants showed a higher rate of decrease in gastric cancer events in Japanese individuals resident in Hawaii than in those who migrated to Brazil, whose rate in turn was similar to the rate of those who stayed in Japan [19]. These differences might indeed be explained by changes occurring in the habitually high dietary salt intake that migrant populations continued or not to maintain in host countries.

Earlier ecological investigations had also shown an adverse effect of high salt consumption on the risk of gastric cancer: The INTERSALT study, including 24 countries, showed a significant direct association between 24 h urinary sodium excretion (a valid proxy for dietary salt intake) and mortality from gastric cancer [20]. Also, the results of the analysis of 65 rural Chinese counties indicated a positive relationship between consumption of salt-preserved vegetables and

mortality from stomach cancer [21]. Similar results were obtained in five Japanese areas, where the authors found a positive association between 24 h urinary sodium excretion and mortality from gastric cancer [22, 23].

While there are remarkable differences in the prevalence of gastric cancer in different countries, a large number of case-control studies suggested an adverse effect of high dietary salt intake or habitual consumption of salted foods on the risk of gastric cancer not only in Asian countries [24, 25], but also in American [26, 27] and European populations [28, 29, 30]. In particular, a most recent European case-control investigation supported the conclusion that high salt consumption is an important risk factor for gastric cancer, with no differences according to HP infection and virulence, tumor site, and histological type [31]. A consensus document of the World Cancer Research Fund International in 2007 supported a relationship between salt consumption and risk of gastric cancer and reported the results of a meta-analysis of the case-control studies available at that time WCRF [13]. In particular, this analysis showed that habitual salted food consumption was positively associated with gastric cancer, with a fivefold increase in risk for each single serving per day.

Finally, as previously mentioned, a number of prospective studies estimated the predictive role of dietary salt intake on the risk of gastric cancer. The majority of these studies were carried out in Japan. Here, a large cohort including 39,065 male and female participants followed for an average of 11 years showed a significant association between total salt intake, assessed by questionnaire, and rate of gastric cancer in men (RR = 2.23) and a positive but not significantly similar trend in women (RR = 1.32) [32]. In addition, another two Japanese investigations detected a similar relationship between high salt intake and rate of gastric cancer, over 11 and 14 years of follow-up, respectively [33, 34]. At variance with these results, the analysis of a cohort of 12,000 male and female participants followed for 15 years in Hawaii demonstrated a positive trend only in women [35]. A large population study carried out in the Netherlands was also not able to detect a significant association between total reported salt intake and risk of gastric cancer (RR = 1.18) [36].

Prospective studies focusing on the consumption of particular salt-rich foods in general demonstrated an adverse effect of elevated consumption on the risk of stomach cancer. Thus, a strong positive association between processed meat consumption and gastric cancer was found in a very large European cohort, including 520,000 male and female participants, in which greater intake was associated with 68 % greater risk compared with lower consumption [37]. A similarly adverse effect of greater processed meat consumption was found in both men and women by the prospective investigation of a large American population sample including 970,000 individuals followed for an average of 14 years [38].

Similar results were found with regard to the consumption of salted fish. Thus, in a sample of 17,600 American men, greater consumption of salted fish correlated with higher mortality for gastric cancer (RR = 1.90) [39]. In a Japanese cohort, greater salted fish consumption was significantly associated with higher gastric cancer incidence in men (RR = 1.77), while in women there was only a

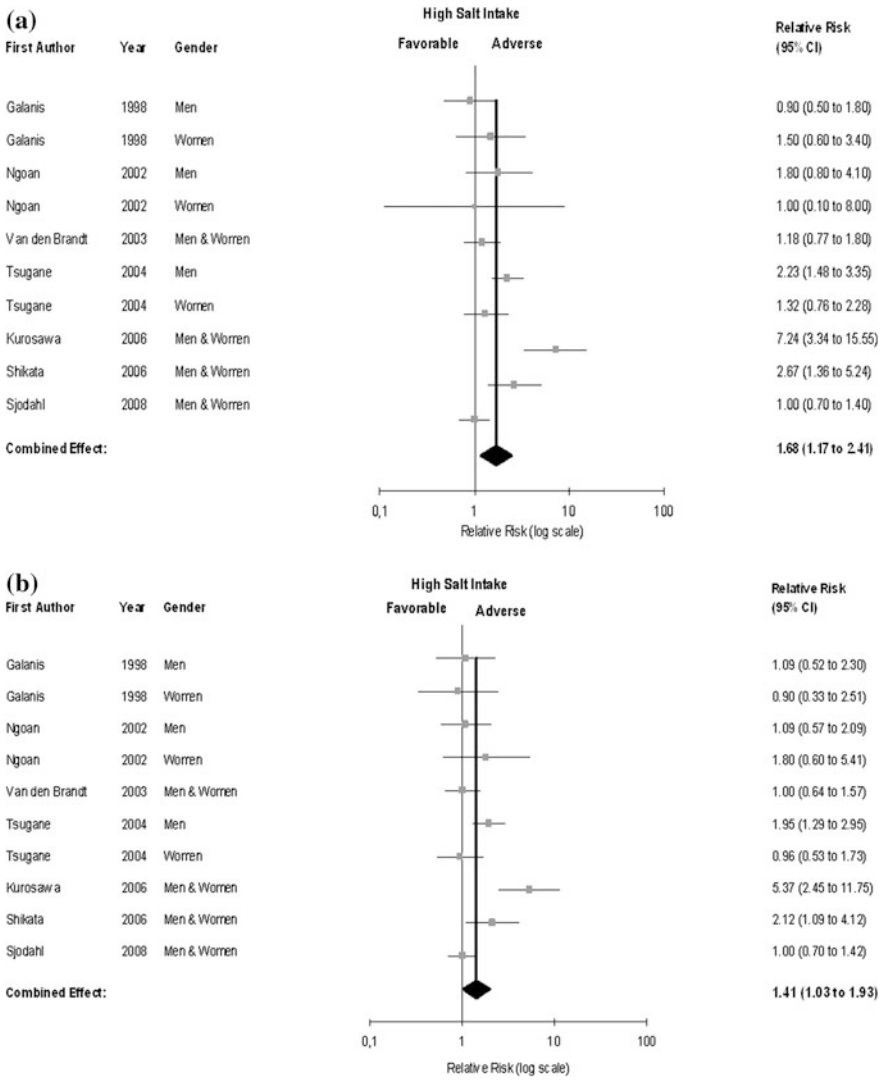

Fig. 1 *Salt intake and risk of gastric cancer*. **a** "*High*" *salt intake*: Forest plot of the risk of gastric cancer associated with "high" salt intake compared to "low" salt intake in 10 population cohorts from 7 published prospective studies. **b** "*Moderately high*" *salt intake*: forest plot 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, $n = 1{,}474$. Results are expressed as relative risk (RR) and 95 % confidence intervals (95 % C.I.). (Adapted from Ref. [14])

nonsignificant trend (RR = 1.17) [32]. However, the authors also reported that higher pickled food intake was associated with greater risk of gastric cancer accidents both in male and in female participants [32]. In another Japanese cohort

composed of over 55,000 atomic bomb survivors, there was also a positive trend between higher intake of pickled foods and risk of gastric cancer after 20 years of follow-up, which, however, did not attain statistical significance (RR = 1.11) [40].

In addition, studies on another common Asian dietary salt-rich food, that is, miso-soup, showed a nonsignificant positive trend between elevated habitual consumption of this type of food and gastric cancer events both in a small American cohort [35] and in a large Japanese population [41].

A recent systematic review of all the prospective studies available has shown unequivocally a direct and significant association between higher salt intake and risk of gastric cancer [14]. This meta-analysis was based on the results of seven studies published between 1998 and 2008 and included 270,000 people and 1,474 events. Pooled estimates based on a follow-up period ranging from 6 to 15 years indicated that there was a graded positive association between habitual salt consumption and incidence of gastric cancer. "High" salt intake and "moderately high" salt intake were associated with 68 and 41 % greater risk of gastric cancer, respectively, compared with "low" salt consumption (Fig. 1). 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. Separate analyses indicated that the 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 significantly associated with 27, 24, and 24 % greater risk of gastric cancer, respectively, whereas high miso-soup consumption showed a similarly nonsignificant trend (RR = 1.05) (Fig. 2).

Finally, Dias-Neto et al. [42] analyzed the association between salted food consumption, preference for salted foods (or the use of table salt), and gastric intestinal metaplasia. The study, that included cohort, case-control and cross-sectional investigations, showed a trend toward an adverse effect of high salt consumption that, however, did not reach statistical significance.

3 Salt Intake and *Helicobacter Pylori* Infection

Helicobacter pylori (HP), infection is one of the main predisposing factors for gastric cancer development. High salt intake increases the colonization by HP [16] and induces mucosal damage on persistent HP infection [16]. A few studies suggested a possible causal link between excess salt intake, HP infection, and carcinogenesis [34, 43, 44].

A cross-sectional study of 634 Japanese men (aged 40–49 years) reported that habitual consumption of salt-rich foods, in particular miso-soup and pickled vegetables, was associated with high prevalence of HP infection [45]. This association was also reported by EUROGAST, an international study that related the rate of national HP infection to the 24 h urinary sodium excretion levels assessed

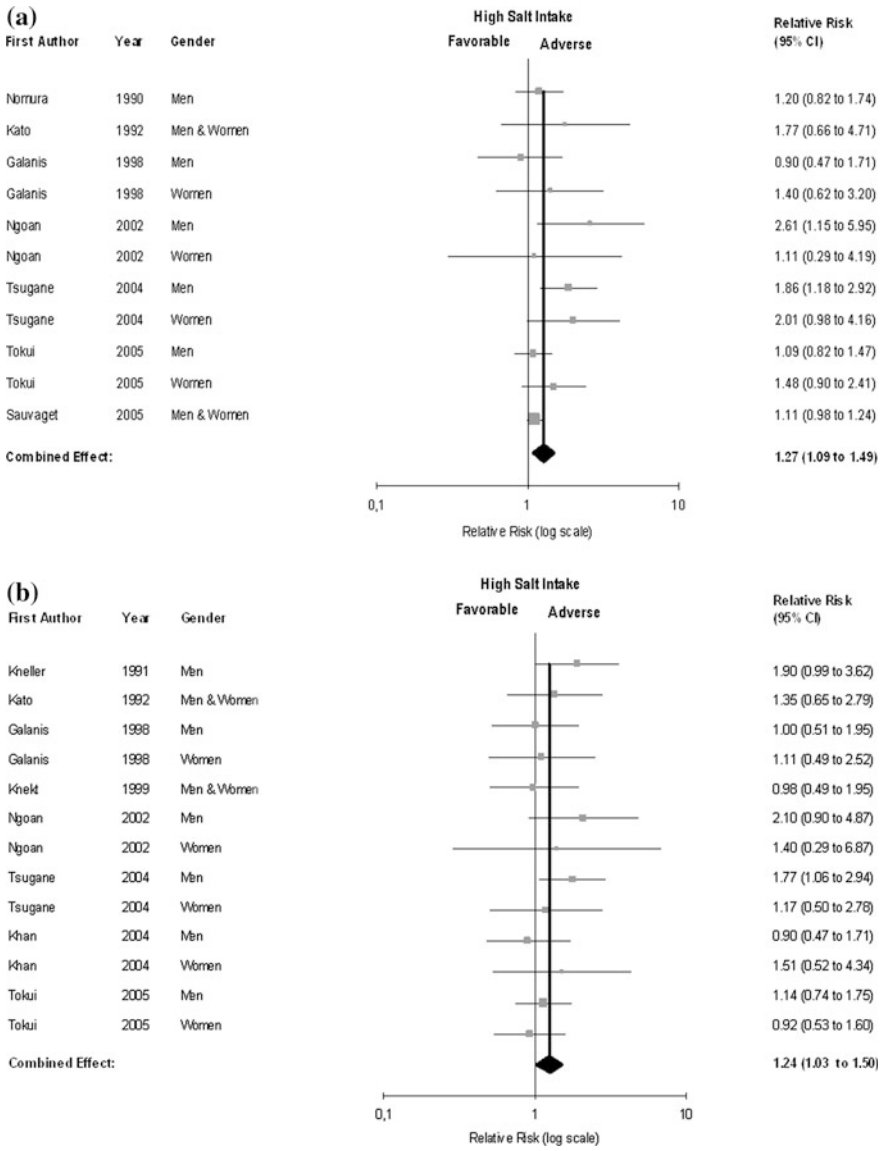

Fig. 2 *Salt-rich foods intake and risk of gastric cancer*. **a** *Pickled foods*: forest plot of the risk of gastric cancer associated with "high" pickled foods intake compared to "low" intake in 11 population cohorts from 7 published prospective studies. Total population, $n = 242{,}568$; events, $n = 2{,}858$. **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, $n = 1{,}447$. **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, $n = 2{,}002$. **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, $n = 3{,}022$. Results are expressed as relative risk (RR) and 95 % confidence intervals (95 % C.I.). (Adapted from Ref. [14])

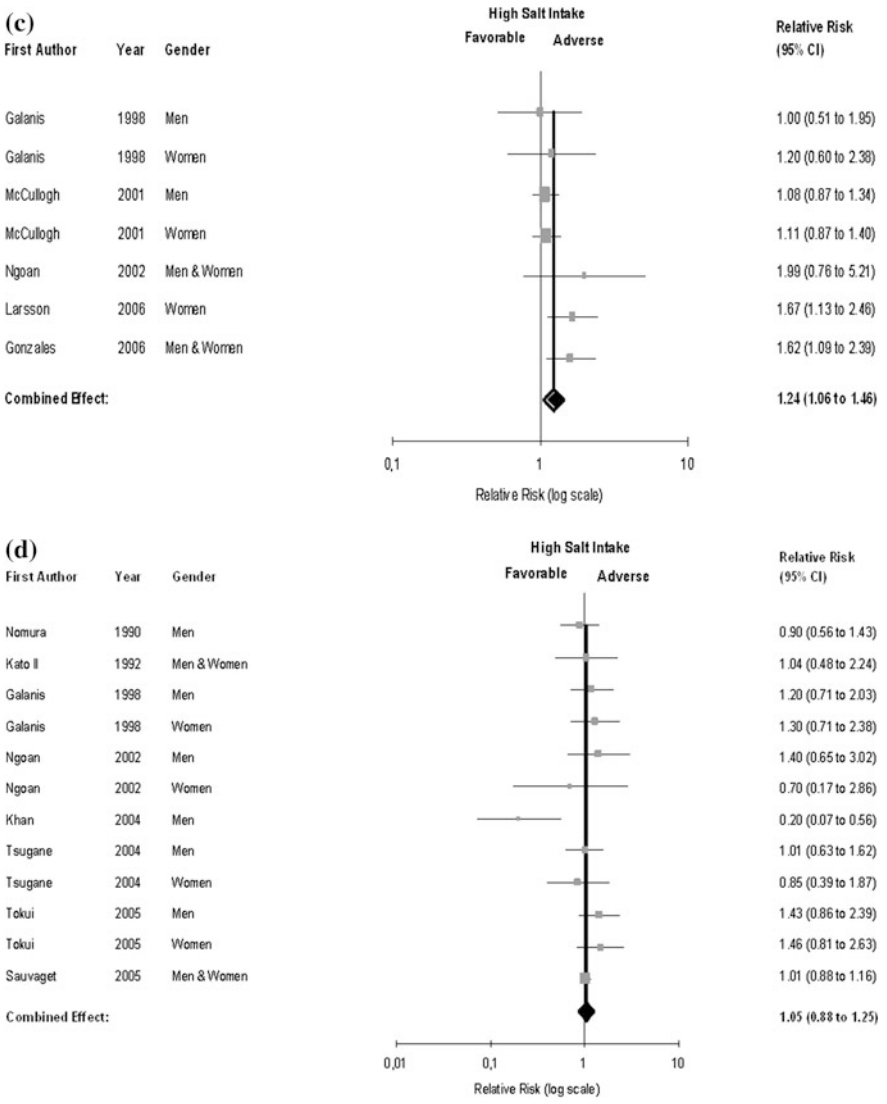

Fig. 2 Continued

by the INTERSALT project. A positive relationship between HP infection rates and urinary sodium excretion was detected in almost of all age and gender categories [46].

Two small case-control studies assessed *Helicobacter pylori* (HP), infection and salt intake in Japanese [44] and Korean [34] samples, after the development of gastric cancer. The authors found that the combination of high salt intake and HP infection was associated with gastric cancer compared to the combination of low

salt diet and no HP infection. In addition, the combination of high salt and HP infection was better associated with the risk of gastric cancer than the combination of *Helicobacter pylori* (HP), infection and low salt intake in a Japanese population sample [44].

The potential association between salted food consumption and HP infection in humans was also evaluated in a Japanese prospective study, which showed a positive association between high salt intake and gastric cancer only in the HP infection-positive group [34]. Moreover, the results indicated a strong effect of high salt intake on gastric carcinogenesis in individuals with both atrophic gastritis and HP infection.

Finally, the synergistic effects of dietary high salt intake and HP infection on gastric carcinogenesis were also found in animal studies. *Helicobacter pylori* (HP), infection exacerbated gastric mucosal damage on a salty diet in mice [47]. Moreover, in a study of Mongolian gerbils with HP infection, the cocarcinogenic effect of a high salt diet was confirmed, and high salt consumption was associated with elevated titers of anti-HP antibodies, hypergastrinemia, and inflammatory cell infiltration [43].

4 Other Biological Mechanisms and Experimental Evidence

A number of experimental studies addressed the question of the possible mechanisms of the adverse effect of excess salt intake toward susceptibility to gastric cancer. As previously mentioned, a powerful interaction has been detected between excess salt intake and HP infection, with high salt intake increasing the rate of colonization of the gastric mucosa by HP [16], enhancing surface mucous cells, and reducing gland mucous cell mucin [43]. A study in rats showed that high dietary salt intake reduced cell yield and produced an increase in the number of S phase cells, susceptible to mutagenesis [17]. In the same species, salt administration induced dose-dependent damage of the surface mucous cell layer and an increase in replicative DNA synthesis [18]. Moreover, in gerbils with HP infection, high dietary salt up-regulated the expression of COX-2 and iNOS [48], potentiated the effects of HP infection, and caused gastric cancer progression [49]. High salt intake was found to potentiate CagA expression (HP gene), increase the capacity of this gene to translocate into gastric epithelial cells, and improve the capacity of HP to alter the function of epithelial cells [50].

In addition, both hypergastrinemia induced by high salt intake in the presence of HP infection [43] and the synergic effect of this chronic hypergastrinemia and HP infection may contribute to parietal cell loss and gastric cancer progression [51].

A number of studies suggested that elevated salt intake may promote and/or enhance the effect of food-derived carcinogens, for example N-nitroso compounds [1, 15, 52], potent carcinogen that may induce tumors in several sites [53], by

affecting the viscosity of the protective mucous barrier [43] and damaging the gastric epithelium.

Finally, some experimental investigations on animal models showed a synergistic effect of high salt intake and chemical carcinogens (MNNG and MNU) in the development of gastric cancer [54, 55].

5 Perspectives

Gastric cancer remains one of the most common forms of cancer worldwide with approximately 870,000 new cases [56, 57] accounting for about 9.9 % of new cancers [58]. 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 [59]. While the worldwide incidence of gastric cancer has declined rapidly throughout recent decades, in particular in Western countries, in China, and other countries in East Asia, the decline has been less substantial than for other countries. In fact, an increased incidence has been observed in the oldest and youngest age groups [60]. Moreover, the age at onset of gastric cancer in the Chinese population is lower than in the West, and this may signal the effect of new environmental factors.

Most adult populations around the world have average daily salt intakes higher than 6 g (MRC [1, 61, 62], and for many in eastern Europe and Asia higher than 12 g [63], while WHO recommendations suggest that average population salt intake should be less than 5 g per day [64]. A population reduction in salt intake is recognized as a global priority for a highly cost-effective prevention of the epidemic of cardiovascular disease in both developed and developing countries [1, 65, 66, 67, 68, 69]. There is ample evidence suggesting the potential for further benefit by this policy in addition to its effects on cardiovascular disease [70].

References

1. Antunes-Rodrigues J, de Castro M, Elias LL et al (2004) Neuroendocrine control of body fluid metabolism. Physiol Rev 84(1):169–208
2. Cordain L, Eaton SB, Miller JB et al (2002) The paradoxical nature of huntergatherer diets: meat-based, yet non-atherogenic. Eur J Clin Nutr 56 Suppl1:S42–S52
3. Eaton SB, Konner M (1985) Paleolithic nutrition. A consideration of its nature and current implications. N Engl J Med 312:283–289
4. Elliott P, Stamler J, Nichols R et al (1996) Intersalt revisited: further analysis of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Coop Res Group. BMJ 312:1249–1253
5. Kupari M, Koskinen P, Virolainen J (1994) Correlates of left ventricular mass in a population sample aged 36 to 37 years. Focus on lifestyle and salt intake. Circulation 89:1041–1050
6. Strazzullo P, D'Elia L, Kandala NB et al (2009) Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ. doi:10.1136/bmj.b4567
7. Cianciaruso B, Bellizzi V, Minutolo R et al (1998) Salt intake and renal outcome in patients with progressive renal disease. Miner Electrolyte Metab 24(4):296–301

8. Cappuccio FP, Kalaitzidis R, Duneclift S et al (2000) Unravelling the links between calcium excretion, salt intake, hypertension, kidney stones and bone metabolism. J Nephrol 13:169–177
9. Devine A, Criddle RA, Dick IM et al (1995) A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. Am J Clin Nutr 62:740–745
10. Stewart BW, Kleihues P (2003) World cancer report. IARC Press, Lyon
11. Kamangar F, Dores GM, Anderson WF (2006) 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 24:2137–2150
12. Parkin DM (2006) The global health burden of infection associated cancers in the year 2002. Int J Cancer 118:3030–3044
13. World Cancer Research Fund/American Institute for Cancer Research (2007) Food, nutrition, physical activity, and the prevention of cancer: a global perspective. AICR, Washington DC
14. D'Elia L, Rossi G, Ippolito R et al (2012) Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies. Clin Nutr. doi:10.1016/j.clnu.2012.01.003
15. Tatematsu M, Takahashi M, Fukushima S et al (1975) 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 55:101–106
16. Fox JG, Dangler CA, Taylor NS et al (1999) High-salt diet induces gastric epithelial hyperplasia and parietal cell loss, and enhances Helicobacter pylori colonization in C57BL/6 mice. Cancer Res 59:4823–4828
17. Charnley G, Tannenbaum SR (1985) Flow cytometric analysis of the effect of sodium chloride on gastric cancer risk in the rat. Cancer Res 45:5608–5616
18. Furihata C, Ohta H, Katsuyama T (1996) Cause and effect between concentration-dependent tissue damage and temporary cell proliferation in rat stomach mucosa by NaCl, a stomach tumor promoter. Carcinogenesis 17:401–406
19. Tsugane S, de Souza JM, Costa ML Jr et al (1990) Cancer incidence rates among Japanese immigrants in the city of Sao Paulo, Brazil, 1969–78. Cancer Causes Control 1:189–193
20. Joossens JV, Hill MJ, Elliott P et al (1996) Dietary salt, nitrate and stomach cancer mortality in 24 countries. European cancer prevention (ECP) and the INTERSALT cooperative research group. Int J Epidemiol 25:494–504
21. Kneller RW, Guo WD, Hsing AW et al (1992) Risk factors for stomach cancer in sixty-five Chinese counties. Cancer Epidemiol Biomarkers Prev 1:113–118
22. Tsugane S, Gey F, Ichinowatari Y et al (1992) Cross-sectional epidemiologic study for assessing cancer risks at the population level. I. Study design and participation rate. J Epidemiol 2:75–81
23. Tsugane S, Gey F, Ichinowatari Y et al (1992) Cross-sectional epidemiologic study for assessing cancer risks at the population level. II. Baseline data and correlation analysis. J Epidemiol 2:83–89
24. Ji BT, Chow WH, Yang G et al (1998) Dietary habits and stomach cancer in Shanghai, China. Int J Cancer 76:659–664
25. Lee JK, Park BJ, Yoo KY et al (1995) Dietary factors and stomach cancer: a case-control study in Korea. Int J Epidemiol 24:33–41
26. Graham S, Haughey B, Marshall J et al (1990) Diet in the epidemiology of gastric cancer. Nutr Cancer 13:19–34
27. López-Carrillo L, López-Cervantes M, Ward MH et al (1999) Nutrient intake and gastric cancer in Mexico. Int J Cancer 83:601–605
28. Coggon D, Barker DJ, Cole RB et al (1989) Stomach cancer and food storage. J Natl Cancer Inst 81:1178–1182
29. La Vecchia C, Negri E, Franceschi S et al (1997) Case-control study on influence of methionine, nitrite, and salt on gastric carcinogenesis in northern Italy. Nutr Cancer 27:65–68

30. Ramón JM, Serra-Majem L, Cerdó C et al (1993) Nutrient intake and gastric cancer risk: a case-control study in Spain. Int J Epidemiol 22:983–988
31. Peleteiro B, Lopes C, Figueiredo C et al (2011) Salt intake and gastric cancer risk according to Helicobacter pylori infection, smoking, tumour site and histological type. Brit J Cancer. doi:10.1038/sj.bjc.6605993
32. Tsugane S, Sasazuki S, Kobayashi M et al (2004) Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. Br J Cancer 90:128–134
33. Kurosawa M, Kikuchi S, Xu J et al (2006) Highly salted food and mountain herbs elevate the risk for stomach cancer death in a rural area of Japan. J Gastroenterol Hepatol 21:1681–1686
34. Shikata K, Kiyohara Y, Kubo M et al (2006) A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. Int J Cancer 119:196–201
35. Galanis DJ, Kolonel LN, Lee J et al (1998) Intakes of selected foods and beverages and the incidence of gastric cancer among the Japanese residents of Hawaii: a prospective study. Int J Epidemiol 27:173–180
36. Van den Brandt PA, Botterweck AA, Goldbohm RA (2003) Salt intake, cured meat consumption, refrigerator use and stomach cancer incidence: a prospective cohort study (Netherlands). Cancer Causes Control 14:427–438
37. González CA, Jakszyn P, Pera G et al (2006) Meat intake and risk of stomach and esophageal adenocarcinoma within the European prospective investigation into cancer and nutrition (EPIC). J Natl Cancer Inst 98(5):345–354
38. McCullough ML, Robertson AS, Jacobs EJ et al (2001) A prospective study of diet and stomach cancer mortality in United States men and women. Cancer Epidemiol Biomarkers Prev 10(11):1201–1205
39. Kneller RW, McLaughlin JK, Bjelke E et al (1991) A cohort study of stomach cancer in a high-risk American population. Cancer 68(3):672–678
40. Sauvaget C, Lagarde F, Nagano J et al (2005) Lifestyle factors, radiation and gastric cancer in atomic-bomb survivors (Japan). Cancer Causes Control 16(7):773–780
41. Tokui N, Yoshimura T, Fujino Y et al (2005) Dietary habits and stomach cancer risk in the JACC study. J Epidemiol 15(Suppl. 2):S98–108
42. Dias-Neto M, Pintalhao M, Ferreira M et al (2010) Salt intake and risk of gastric intestinal metaplasia: systematic review and meta-analysis. Nutr Cancer 62:133–147
43. Kato S, Tsukamoto T, Mizoshita T et al (2006) 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 119:1558–1566
44. Machida-Montani A, Sasazuki S, Inoue M et al (2004) Association of Helicobacter pylori infection and environmental factors in non-cardia gastric cancer in Japan. Gastric Cancer 7:46–53
45. Tsugane S, Tei Y, Takahashi T et al (1994) Salty food intake and risk of Helicobacter pylori infection. Jpn J Cancer Res 85:474–478
46. Beevers DG, Lip GY, Blann AD (2004) Salt intake and Helicobacter pylori infection. J Hypertens 22:1475–1477
47. Shimizu N, Kaminishi M, Tatematsu M et al (1998) 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 123:63–69
48. Toyoda T, Tsukamoto T, Hirano N et al (2008) 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 23:593–599
49. Nozaki K, Shimizu N, Inada K et al (2002) Synergistic promoting effects of Helicobacter pylori infection and high-salt diet on gastric carcinogenesis in Mongolian gerbils. Jpn J Cancer Res 93:1083–1089

50 Loh JT, Torres VJ, Cover TL (2007) Regulation of Helicobacter pylori cagA expression in response to salt. Cancer Res 67:4709–4715
51. Wang TC, Dangler CA, Chen D et al (2000) Synergistic interaction between hypergastrinemia and Helicobacter infection in a mouse model of gastric cancer. Gastroenterology 118:36–47
52. Takahashi M, Nishikawa A, Furukawa F et al (1994) Dose-dependent promoting effects of sodium chloride (NaCl) on rat glandular stomach carcinogenesis initiated with N -methyl-N'-nitro- N -nitrosoguanidine. Carcinogenesis 15:1429–1432
53. Tricker AR, Preussmann R (1991) Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential. Mutat Res 259:277–289
54. Takahashi M, Hasegawa R (1985) Enhancing effects of dietary salt on both initiation and promotion stages of rat gastric carcinogenesis. Princess Takamatsu Symp 16:169–182
55. Leung WK, Wu KC, Wong CY et al (2008) Transgenic cyclooxygenase-2 expression and high salt enhanced susceptibility to chemical-induced gastric cancer development in mice. Carcinogenesis 29:1648–1654
56. Ferlay J, Bray F, Parkin DM, Pisani P (eds) (2001) Gobocan 2000: cancer incidence and mortality worldwide (IARC cancer bases no. 5). IARC Press, Lyon
57. Lau M, Le A, El-Serag HB (2006) Noncardia gastric adenocarcinoma remains an important and deadly cancer in the United States: secular trends in incidence and survival. Am J Gastroenterol 101:2485–2492
58. Parkin DM (1998) Epidemiology of cancer: global patterns and trends. Toxicol Lett 102–103:227–234
59. Parkin DM, Pisani P, Ferlay J (1999) Global cancer statistics. CA Cancer J Clin 49:33–64
60. Jemal A, Siegel R, Ward E et al (2006) Cancer statistics. CA Cancer J Clin 56(2):106–130
61. Donfrancesco C, Ippolito R, Lo Noce C et al (2012) Excess dietary sodium and inadequate potassium intake in Italy: results of the MINISAL study. Nutr Metab Cardiovasc Dis. doi: 10.1016/j.numecd.2012.04.004
62. MRC, Human Nutrition Research, National Centre for Social Research (2008) An assessment of dietary sodium levels among adults (aged 19–64) in the UK general population in 2008, based on analysis of dietary sodium in 24 hour urine samples. 2008/0730 http://www.food.gov.uk/news/pressreleases/2008/jul/sodiumrep08. Accessed 22 July 2008
63. Brown IJ, Tzoulaki I, Candeias V et al (2009) Salt intakes around the world: implications for public health. Int J Epidemiol 38:791–813
64. World Health Organization (2003) Diet, nutrition and the prevention of chronic diseases: report of a joint WHO/FAO expert consultation
65. Campbell N, Correa-Rotter R, Neal B et al (2011) New evidence relating to the health impact of reducing salt intake. Nutr Metab Cardiovasc Dis 21(9):617–619
66. Cappuccio FP, Capewell S, Lincoln P et al (2011) Policy options to reduce population salt intake. BMJ 343:d4995
67. Geneau R, Stuckler D, Stachenko S et al (2010) Raising the priority of preventing chronic diseases: a political process. Lancet 376(9753):1689–1698
68. Strazzullo P, Cairella G, Campanozzi A et al (2012) Population based strategy for dietary salt intake reduction: Italian initiatives in the European framework. Nutr Metab Cardiovasc Dis 22(3):161–166
69. World Health Organization (2007) Reducing salt intake in populations. Report of a WHO Forum and Technical Meeting, Geneva
70. Capewell S, O'Flaherty M (2011) Rapid mortality falls after risk-factor changes in populations. Lancet. doi:10.1016/S0140-6736(10)62302-1