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Nutrition and stomach cancer

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Epidemiologic evidence on the relation between nutrition and stomach cancer is reviewed. Stomach cancer shows a distinct international variation and dramatic worldwide decline. These descriptive features suggest that dietary factors are important in determining the risk of stomach cancer. The authors assessed relevant data regarding specific dietary hypotheses in the etiology of stomach cancer. A negative association with fresh vegetables and fruits is highly consistent in numerous case-control studies in different populations. Both epidemiologic and experimental data suggest that vitamins C and carotenoids lower risk of stomach cancer. Evidence is sparse and inconsistent as to protective effects of vitamin E and selenium. Epidemiologic studies have not lent, and will not provide, supportive evidence for an etiologic role of nitrate intake. High salt intake has been associated with an increased risk in many case-control studies and limited cohort studies. Taken together with animal data, it is considered that high salt intake is a risk factor for stomach cancer. Both epidemiologic and experimental data are inconclusive as to whether high-starch diets confer an increased risk. Cohort studies using quantitative dietary assessment and biologic measurement of micronutrients are needed for further understanding of etiologic roles of dietary factors in the causation of stomach cancer. *Cancer Causes and Control* 1996, 7, 41-55

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Introduction

Although stomach cancer has declined dramatically worldwide,[1] this cancer is the second most common cancer in the world following lung cancer.[2] Stomach cancer mortality and incidence show a distinct geographic variation with the highest rates in Japan, China, and some countries in South America, and the lowest rates in Australia, Canada, and United States.[2,3] Migrants from high risk to low risk countries or areas tend to maintain the high risk characteristic of the populations of origin, and the offspring acquire a risk closer to those of the host countries.[4,5] Low socioeconomic status generally is associated with high risk.[6] These descriptive features suggest that dietary and lifestyle factors are important in the etiology of stomach cancer. Since ingested foods come into prolonged contact with the gastric mucosa, dietary factors are of primary interest.

Smoking and *Helicobacter pylori* infection are currently accepted as risk factors for stomach cancer. Prospective studies have observed an excess, although modest, risk of stomach cancer among smokers with a dose-response relationship in several studies.[7-10] A positive association between *H. pylori* infection and stomach cancer has been reported in between-population studies[11,12] and cohort studies of individuals.[13-15] *H. pylori* also is shown to be linked with precursor lesions such as chronic atrophic gastritis[12] and intestinal metaplasia.[16] The infection, however, is highly prevalent even in populations at low risk of stomach cancer[11] or with a low prevalence of intestinal metaplasia,[17] and thus *H. pylori* infection itself would not be sufficient in determining stomach cancer risk.[18]

In this paper, we systematically and comprehensively

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review epidemiologic evidence regarding specific dietary hypotheses in the etiology of stomach cancer. The dominant dietary hypothesis is that fresh vegetables and fruits or micronutrients rich in these foods are protective against stomach cancer. The possible intragastric formation of carcinogenic *N*-nitroso compounds is most relevant to this hypothesis. Another hypothesis is that high-salt foods or excessive salt intake increases the risk of stomach cancer. High-starch diets also have been suspected as a possible etiologic candidate. We also discuss dietary factors uniquely associated with stomach cancer in certain populations. Since epidemiologic features appear to be different between intestinal and diffuse types and between cardiac and distal gastric cancers,[18] we refer briefly to relevant data for these subtypes.

Vegetables and fruit

Ecologic studies

Although vegetable or fruit consumption is not correlated appreciably with stomach cancer rates in different countries,[19] correlation studies within countries have provided a limited evidence for the hypothesis that vegetables and fruit may be protective. The consumption of fresh vegetables and fruits was higher in villages at low risk of stomach cancer than in villages at high risk in Columbia.[20] Stomach cancer mortality rates in 65 counties in China were correlated negatively with the consumption of green vegetables ($r = -0.44$ in males and $r = -0.36$ in females), but not with fruit consumption.[21] The decline in stomach cancer mortality in Japan parallels the increasing consumption of fruit since the 1950s.[22]

Case-control studies

Results related to vegetable and fruit consumption in different countries are summarized in Table 1.[23-42] Two historic case-control studies, one by Wynder *et al*[43] and the other by Acheson and Doll,[44] are not informative on this topic; the authors simply noted that no significant association was found between dietary variables studied and stomach cancer risk, without presenting relevant data. Most case-control studies measured relatively recent diets, prior to the onset of stomach cancer, and few studies ascertained food consumption in the distant past.[34,42] Dietary methods used in these studies varied substantially from the simple measurement of consumption frequency of broad food groups[23,31-33] to the quantitative measurement of numerous individual foods.[29,34,40,41] With few exceptions,[31,33,38] most studies have found a decreased risk with vegatables, especially those consumed raw. In a study of Japanese in Hawaii,[25] a 40 to 50 percent decrease in the risk of stomach cancer was observed among those with the highest consumption of each Western-type vegetable (including tomatoes, celery, corn, lettuce, and onions), except for lettuce. In a Polish study by Boeing *et al*,[39] eight of 11 individual vegetables including onions, tomatoes, and lettuce were related to a decreased risk. A decreased risk associated with fruit consumption is more consistent than that observed for vegetables.

Considering methodologic difficulties in dietary assessment and the relatively homogeneous nature in dietary intake in the same region, it is remarkable that similar findings for fresh vegetables and fruits have been reproduced in many studies using different methods in different populations. Total caloric intake or total food consumption was adjusted for in three[29,38,40] of seven studies employing quantitative dietary assessment. Not allowing for total caloric intake adds to an extraneous variation in vegatable and fruit consumption, thereby attenuating the true association.[45] Nonadjustment for total caloric intake is thus unlikely to result in such a consistent association with fresh vegetables and fruits. In studies using multivariate analysis,[30,35,38,41,42] decreased risk associated with fresh vegetables or fruits was generally independent of other dietary risk factors such as salty foods and/or cereal consumption. Further, a negative association with fresh vegetables and fruit does not seem to be different between intestinal and diffuse types,[25,27,39,46] nor between cardiac and other gastric cancers.[47]

Because animal and *in vitro* experiments have suggested that garlic and onion extracts and their constituents (*e.g.*, allyl sulfides) inhibit the development of several types of tumors,[48] a protective role of garlic and allium vegetables has drawn interest in the etiology of stomach cancer. In China,[49] total consumption of five allium vegetables (garlic, garlic stalks, leeks, Chinese chives, and onions) was related to a substantial decrease in the risk; relative risk (RR) for the highest *cf* lowest consumption was 0.4 (95 percent confidence interval [CI] = 0.3-0.6). Each allium vegetable also was associated with a decreased risk although the association with onions was relatively weak. The use of garlic and onions as condiments was related weakly, but significantly, to a decreased risk (P trend = 0.04) in an Italian study.[36] A protective effect of garlic was not clear in Sweden,[42] but garlic was rarely consumed in the study population. A fairly large decrease in the risk also was observed among those with high consumption of leeks in Belgium[40] and Sweden.[42] Onions are probably the most popular allium vegetable in many countries, but the findings on onions are inconsistent. A decreased risk associated with onion consumption was reported in Hawaii (USA),[25] Greece,[30] Poland,[39] and Belgium,[40] but not in Japan,[27] Spain,[38] and Sweden.[42] The content of possible preventive compounds probably varies with types of allium vegetables as well as with cooking methods. The association with an individ-

Table 1. Vegetables, fruit, and stomach cancer in case-control and cohort studies

Study (ref.) Year	Location Population	Comparison	Type of vegetables	RR[a]	(CI)[b]	Type of fruit	RR[a]	(CI)[b]
Case-control								
Hirayama [23] 1971	Japan	*Frequency distribution*	*Green-yellow vegetables*	*Decrease*	N/S[c]	—	—	—
Graham, *et al* [24] 1972	USA	Frequency distribution	Raw vegetables	Decrease	$P < 0.05$	Fresh fruit	—	N/S
Haenszel, *et al* [25] 1972	Hawaii, USA Japanese	2 levels of frequency	Western types	0.4	$P < 0.05$	Selected fruit	0.9	N/S
Bjelke[26] 1974	Norway	Frequency score	Total vegetables	Decrease	—	Various fruit	Decrease	—
	USA		Total vegetables	Decrease	—	—	—	—
Haenszel, *et al* [27] 1976	Japan	3 levels of frequency	Celery	0.6	$P < 0.01$	Selected fruit	0.7	$P < 0.05$
			Lettuce	0.7	$P < 0.01$			
Correa, *et al* [28] 1985	USA White	Quartiles of frequency score	Total vegetables	0.9[d]	(0.6-1.4)	Total fruit	0.5	(0.2-0.9)
	USA Black		Total vegetables	0.5	(0.3-1.0)	Total fruit	0.3	(0.2-0.7)
Risch, *et al* [29] 1985	Canada	Per 100 g/day	Pale-green vegetables	0.3	(0.1-1.1)	Citrus fruit	0.8	(0.6-0.9)
			Cruciferous vegetables	0.7	(0.4-1.1)			
Trichopoulos, *et al* [30] 1985	Greece	Frequency score	Salad vegetables	Decrease	P trend < 0.01	Citrus fruit	Decrease	P trend < 0.01
			Total vegetables	Decrease	P trend < 0.01			
Jedrychowski, *et al* [31] 1986	Poland	3 levels of frequency	Salad vegetables	1.0	(0.4-2.7)	Fruit	0.3	(0.1-0.6)
			Cooked vegetables	0.6	(0.3-1.5)			
La Vecchia, *et al* [32] 1987	Italy	Tertiles of frequency	Green vegetables	0.3	P trend < 0.01	Fresh fruit	0.5	P trend < 0.01
						Citrus fruit	0.6	P trend < 0.05
Kono, *et al* [33] 1988	Japan	3 levels of frequency	Raw vegetables	0.8	N/S trend	Mandarin	0.6	P trend $= 0.05$
			Green-yellow vegetables	1.3	N/S trend	Other fruit	0.6	P trend $= 0.07$
You, *et al*[34] 1988	China	Quartiles of amount	Fresh vegetables	0.4	(0.3-0.6)	Fresh fruit	0.6	(0.4-0.8)
Coggon, *et al* [35] 1989	England, UK	3 levels of frequency	Salad in summer	0.2	(0.1-0.5)	Fresh/frozen fruit	0.4	(0.2-0.8)
			Salad in winter	0.3	(0.1-0.5)			
Buiatti, *et al* [36] 1989	Italy	Tertiles of frequency	Raw vegetables	0.6	P trend < 0.001	Citrus fruit	0.6	P trend < 0.001
			Cooked vegetables	1.1	N/S trend	Other fresh fruit	0.4	P trend < 0.001

Continued...

Table 1. Continued

Study (ref.) Year	Location Population	Comparison	Type of vegetables	RR[a]	(CI)[b]	Type of fruit	RR[a]	(CI)[b]
Boeing, *et al*[37] 1991	Germany	Tertiles of amount	Raw vegetables	0.6	(0.4-1.0)	Total fruit	0.6	(0.4-0.9)
			Total vegetables	0.9	(0.5-1.4)	Citrus fruit	0.4	(0.3-0.7)
González, *et al*[38] 1991	Spain	Quartiles of amount	Raw vegetables	0.8	N/S trend	Citrus fruit	1.0	N/S trend
			Cooked vegetables	0.5	P trend = 0.02	Other fresh fruit	0.6	P trend < 0.01
Boeing, *et al*[39] 1991	Poland	3 levels of frequency	Total vegetables	0.6	P trend < 0.01	Total fruit	0.7	P trend < 0.01
Tuyns, *et al*[40] 1992	Belgium	Levels of amount	Raw vegetables	0.4[4]	P trend < 0.01	Fresh fruit	0.6[4]	P trend < 0.01
			Cooked vegetables	0.3[4]	P trend < 0.01	Citrus fruit	0.8[3]	N/S trend
Ramón, *et al*[41] 1993	Spain	Quartiles of amount	Raw vegetables	0.6	P trend < 0.01	Total fruit	0.7	P trend < 0.05
			Total vegetables	0.7	N/S trend	Citrus fruit	0.7	P trend < 0.01
Hansson, *et al*[42] 1993	Sweden[c]	Levels of frequency	Total vegetables	0.5[4]	(0.3-0.8)	Apples and pears	0.6[4]	(0.4-1.0)
						Citrus fruit	0.7[5]	(0.4-1.2)
Cohort								
Hirohata[50] 1983	Japan	Mean intake	Green-yellow vegetables	—	N/S	—	—	—
			Other vegetables	—	N/S			
Hirayama[8] 1990	Japan	4 levels of frequency	Green-yellow vegetables	0.7	P trend < 0.01	—	—	—
Chyou, *et al*[51] 1990	Hawaii, USA Japanese	4 levels of amounts	Total vegetables	0.7	P trend < 0.01	Total fruit	0.8	N/S trend
			Green vegetables	0.7	P trend = 0.06			
Kneller, *et al*[9] 1991	USA	Quartiles of amount	Total vegetables	0.9	(0.5-1.8)	Total fruit	1.5	(0.8-2.9)
			Cruciferous vegetables	1.3	(0.7-2.7)			
Kato, *et al*[10] 1992	Japan	3 levels of frequency	Green-yellow vegetables	1.5	(0.8-3.1)	Fruit	1.9	(1.0-3.6)
			Other vegetables	1.2	(0.6-2.3)			

[a] RR = relative risk, for the highest *cf* lowest level. Numbers of categories are presented in brackets when differently categorized.
[b] CI = 95 percent confidence interval.
[c] N/S = not significant.
[d] Comparison of above *cf* below median.

ual vegetable is less informative unless the ingested form is ascertained.

Cohort studies

A negative association between vegetables and stomach cancer is less pronounced in limited cohort studies (Table 1),[8-10,50,51] but none of the studies investigated the association with fresh vegetables specifically. Three of these studies,[9,10,50] which found no measurable inverse relation to any group of vegetables studied, were based on small numbers (57 to 75) of deaths from stomach cancer. The 24-hour recall method was employed in studies by Hirohata[50] and Chyou *et al*[51] while the usual consumption frequency was ascertained in the other studies.[8-10]

Three of these cohort studies[9,10,51] also examined the relation to fruit intake, but lent little support to an inverse association with fruit. Even a significant increase in risk was observed in relation to apple consumption in high season[9] and fruit consumption.[10] In the cohort of Japanese men in Hawaii, Nomura *et al*[7] also reported an insignificant, inverse association between the usual consumption frequency of fruit and stomach cancer risk, showing an RR of 0.8 (CI = 0.5-1.3) for the comparison of ≥ 5 times *cf.* ≤ 1 time per week.

Micronutrients

Vegetables and fruits are rich in vitamin C and carotenoids, and vegetables also are a major dietary source of vitamin E and selenium. All these micronutrients have antioxidative properties with different mechanisms, and may be protective against stomach cancer.[52,53] Vitamins C and E inhibit the formation of *N*-nitroso compounds, potential carcinogens to human stomach.[54,55] Thus, potential protective effects of these micronutrients have been of particular interest not only for stomach cancer but also for other cancers.

Ecologic studies

The geographic correlation study in China[21] reported a moderate, negative correlation with serum levels of vitamin C and β-carotene ($r = -0.06$ to -0.26), and a more prominent correlation with serum selenium levels ($r = -0.33$ in males and $r = -0.39$ in females). In this study, serum α-tocopherol levels showed a weak, positive correlation with stomach cancer mortality.

Case-control studies

Not many studies have estimated dietary intake of micronutrients, but case-control studies have shown a consistent negative association of dietary intakes of vitamin C and carotenoids with stomach cancer as summarized in Table 2.[28,29,32,34,37,56-60] Total caloric intake was adjusted for in most of the recent studies,[56-60] and total food consumption in a Canadian study.[29] Retinol intake was not associated clearly with stomach cancer risk, and one study found a significantly increased risk with retinol intake.[57] Dietary intake of vitamin E was estimated in six studies,[29,56-60] and two of them[56,60] found a significant inverse relation.

Two studies[61,62] examined cross-sectionally the relation between serum micronutrient levels and precancerous gastric lesions. While serum vitamin C levels did not vary among those with different gastric lesions in Columbia,[61] subjects having intestinal metaplasia had lower vitamin C levels than those with superficial gastritis or Chronic atrophic gastritis in China.[62] Lower serum carotenoid levels were associated with gastric dysplasia[61] or intestinal metaplasia.[62] There was virtually no difference in serum retinol or vitamin E levels according to precancerous lesions in these studies.

Cohort studies

A cohort study of Japanese men in Hawaii,[51] without adjustment for total caloric intake, reported lower dietary intakes of vitamin C, β-carotene, and other carotenes among those developing stomach cancer than among cancer-free men, but the differences were not statistically significant ($P = 0.11$-0.21). Retinol intake was slightly higher among men developing stomach cancer, and there was no difference in vitamin E intake.[51]

Several cohort studies[63-66] have compared baseline serum levels of micronutrients between cases subsequently developing stomach cancer or those dying from this cancer, compared with appropriately selected control subjects (Table 3). Vitamin C levels were measured only in the cohort of Swiss men,[66] and stomach cancer cases had a 20 percent lower concentration of vitamin C ($P < 0.05$). Serum concentrations of β-carotene or total carotene were 10 to 30 percent lower among male cases of stomach cancer,[63,66] and the difference was significant in the Swiss cohort.[66] There was no material difference in either retinol[63,65,66] or vitamin E[63-66] between stomach cancer cases and controls.

Dietary assessment of selenium intake is difficult because selenium content of a specific food depends on the selenium content of the soil where it is produced.[52] Three prospective studies[67-69] have addressed the association between serum or toenail selenium levels and stomach cancer. Serum selenium levels were not associated with stomach cancer risk in Japanese men in Hawaii (P trend = 0.88).[67] A Finnish study[68] observed a decreased risk for both men and women; RRs for the highest *cf* lowest quintile were 0.1 in men (P trend = 0.002) and 0.3 in women (P trend = 0.15). These inverse relations remained after adjustment for smoking and serum retinol and α-tocopherol. In the Netherlands,[69] toenail selenium was associated with a reduced risk among men with a RR

Table 2. Dietary intake of vitamin C, retinol, and carotenoids and stomach cancer risk in case-control studies

Study (ref.) Year	Location Population	Comparison	Relative risk (95% confidence interval)			Adjustment for total calories
			Vitamin C	Retinol	Carotenoids	
Correa, *et al* [28] 1985	USA White USA Black	Top *cf* bottom quartile	0.5 (0.3-1.0) 0.3 (0.2-0.7)	—	0.7 (0.4-1.1)[a] 1.1 (0.7-1.7)[a]	(−)
Risch, *et al* [29] 1985	Canada	Per 1 g/day for vitamin C Per 10 KIU/day for vitamin A	0.4 (0.2-1.2)	0.9 (0.4-1.8)	0.3 (0.2-0.7)	(+)[b]
La Vecchia, *et al* [32] 1987	Italy	Top *cf* bottom tertile	0.5 (P trend < 0.001)	0.9 (N/S trend)	0.4 (P trend < 0.001)	(−)
You, *et al* [34] 1988	China	Top *cf* bottom quartile	0.5 (0.3-0.6)	1.0 (0.7-1.4)	0.5 (0.3-0.6)	(−)
Buiatti, *et al* [56] 1990	Italy	Top *cf* bottom quintile	0.5 (0.4-0.7)	1.0 (0.7-1.3)	0.6 (0.5-0.9)	(+)
Graham, *et al* [57] 1990	USA Male USA Female	Per standard deviation	— (N/S) — (N/S)	1.5 (1.2-2.0) 1.4 (1.0-2.0)	0.6 (0.5-0.8) 0.7 (0.5-1.10)	(+)
Boeing, *et al* [37] 1991	Germany	Top *cf* bottom quintile	0.4 (0.2-0.8)	—	0.8 (0.5-1.5)	(−)
Ramón, *et al* [58] 1993	Spain	Top *cf* bottom quartile	0.3 (0.1-0.9)	—	0.6 (0.2-1.2)	(+)
González, *et al* [59] 1994	Spain	Top *cf* bottom quartile	0.6 (P trend = 0.02)	1.5 (P trend = 0.15)	0.7 (P trend = 0.31)	(+)
Hansson, *et al* [60] 1994	Sweden	Top *cf* bottom quartile	0.4 (0.3-0.6)	0.8 (0.6-1.3)	0.5 (0.4-0.8)	(+)

[a] Comparison of above *cf* below median.
[b] Adjusted for total food consumption.
N/S = not significant.

Table 3. Serum β-carotene and retinol and subsequent risk of stomach cancer in cohort studies

Study (ref.) Year	Location Population	No. of cases/ controls	% Mean difference[a]			
			β-carotene		Retinol	
Nomura, *et al*[63] 1985	Hawaii, USA Japanese men	70/302	−21	$P>0.10$	+1	$P>0.50$
Wald, *et al*[64] 1988	UK, Men	13/26	−27	N/S[b]	—	
Knekt, *et al*[65] 1990	Finland Men	48/90	−10	$P=0.39$	−3	$P=0.38$
	Women	28/48	+28	$P=0.11$	+1	$P=0.91$
Stähelin, *et al*[66] 1991	Switzerland Men	20/2,421	−36[c]	$P<0.01$	−8	N/S

[a] Case-control difference; median was used by Nomura *et al.*[63]
[b] N/S = not significant.
[c] Total carotene.

of 0.4 (CI = 0.2-1.0) at the highest *cf* lowest quintile after allowance for smoking and dietary intake of β-carotene and vitamin C, but no inverse relation was found among women.

Intervention trials

Three randomized intervention trials[70-72] have reported relevant data. Two studies[70,71] were carried out in Linxian, a rural county in China, where the inhabitants are marginally deficient in several micronutrients. In one of them,[70] nearly 30,000 adults were allocated to one of the four combination supplements of micronutrients (retinol and zinc; riboflavin and niacin; vitamen C and molybdenum; and β-carotene, vitamin E, and selenium), and were followed-up for a period of five years. A 16 percent reduction in incidence (CI = 0-29 percent) and 21 percent reduction in mortality (CI = 1-36 percent) were recorded among those receiving the combination supplements of β-carotene, vitamin E, and selenium, but no decrease or increase in the risk was found among those taking other combinations of supplements. Another study in China[71] followed-up more than 3,000 adults with cytologically diagnosed esophageal dysplasia, who were allocated either to the group of daily supplement with 14 vitamins and 12 minerals or to the placebo group, over a six-year period. Insignificantly larger numbers of stomach cancer incidence (96 *cf* 81) and death (42 *cf* 35) were observed among the supplement group.

The third study[72] was based on about 30,000 male smokers in southern Finland, who were assigned to one of the four groups with supplements of β-carotene, vitamin E, β-carotene plus vitamin E, and placebo. Stomach cancer incidence was slightly higher, but insignificantly, among men receiving β-carotene than those not (70 *cf* 56 cases), and among men with vitamin E supplement than those without (70 *cf* 56 cases).

These studies obviously cannot address the long-term effects of micronutrients on stomach cancer risk. The favorable results from a study in China[70] are difficult to generalize to populations with generally higher intakes of micronutrients.

Animal and mechanistic studies

It is well-established that vitamins C and E inhibit the intragastric formation of *N*-nitroso compounds in humans as well as in animals.[54,55] Vitamin C reduces nitrite to nitric oxide most effectively at pH 3 to pH 5, the range of normal stomach contents after ingestion of a meal, thereby inhibiting nitrosation in an aqueous phase. Since vitamin E inhibits nitrosation in the lipid phase, a combination of vitamins C and E seems to be particularly effective in inhibiting nitrosation in the lipid-water mixtures, which normally are produced by omnivorous diets.

Protective effects of vitamin C also may be ascribed to its effect as an antioxidant.[53] Vitamin E functions as a lipid antioxidant in cells, scavenging free radicals and lipid peroxides.[52] An antioxidative effect of selenium is linked with the activity of glutathione peroxidase, which acts against oxidative tissue damage.[52] β-carotene and other carotenoids are also potent antioxidants, and may exert an anticancer effect by scavenging oxygen radicals.[73] Although epidemiologic evidence is not supportive, it is possible that vitamin A (retinol) converted from carotenoids may exert a protective effect; retinol and other retinoids play an important role in the regulation of cell differentiation, and may prevent malignant transformation of cells.[74]

Animal studies indicate that dietary vitamin C,[55] vitamin E,[55] and selenium,[75] each inhibit the development of several types of tumors, but no animal experiment has reported that these micronutrients inhibit carcinogenesis in the glandular stomach. Carotenoids inhibit carcino-

Table 4. Salty foods, salt intake, and stomach cancer risk in case-control and cohort studies

Study (ref.) Year	Location Population	Variable	Comparison	RR[a]	(CI)[b]
Case-control					
Hirayama[23] 1971	Japan	Salted vegetables	Frequency distribution	Increase	$P < 0.05$
Haenszel, *et al*[25] 1972	Hawaii, USA Japanese	Salted/dried fish Salted vegetables	Levels of frequency	2.6[4] 2.7[3]	$P < 0.05$ $P < 0.05$
Bjelke[26] 1974	Norway USA	Salted fish Smoked fish	Frequency score	Increase Increase	
Haenszel, *et al*[27] 1976	Japan	Salted/dried fish Salted vegetables	3 levels of frequency	1.2 0.8	N/S[c] $P < 0.05$
Correa, *et al*[28] 1985	USA White	Smoked foods Cured meat	Above *cf* below median in frequency	1.2 0.7	N/S N/S
	Black	Smoked foods Cured meat		1.7 2.3	(1.0-2.9) (1.1-4.9)
Risch, *et al*[29] 1985	Canada	Smoked meats Smoked fish Salt intake	Per 100 g/day	2.2 2.0 —	(1.2-4.2) (0.3-12.2) N/S
Jedrychowski, *et al*[31] 1986	Poland	Sausages/meat products	Frequency	—	N/S
LaVecchia, *et al*[32] 1987	Italy	Ham Sausages Table salt	3 levels of frequency	1.5 1.3 1.5	P trend < 0.05 N/S trend N/S trend
Kono, *et al*[33] 1988	Japan	Salty foods	3 levels of frequency	1.4	N/S trend
You, *et al*[34] 1988	China	Salted fish Salted vegetables Household salt use	Levels of amount	1.4[3] 1.1[2][d] 1.1[4]	(0.8-1.5) (0.7-1.8) (0.8-1.4)
Tuyns, *et al*[93] 1988	Belgium	Table salt	3 levels of frequency	1.8	(1.2-2.8)
Coggon, *et al*[35] 1989	England	Salty foods and table salt	3 levels of frequency score	3.0	(1.3-7.1)
Buiatti, *et al*[36] 1989	Italy	Salted/dried fish Table salt	Levels of frequency score	1.4[3] 1.5[2]	P trend < 0.001 (1.3-1.9)
Graham, *et al*[57] 1990	USA Male Female	Salt intake Salt intake	Quartiles of amount	3.1 4.7	(1.7-5.8) (2.3-9.6)
Boeing, *et al*[37] 1991	Germany	Preserved fish Cured meats Table salt	Tertiles of amount	1.0 1.7 —	(0.6-1.5) (1.1-2.8) N/S
González, *et al*[38] 1991	Spain	Preserved fish Cured meats	Levels of amount	1.8[2] 1.5[4]	P trend < 0.05 P trend $= 0.07$
Boeing, *et al*[39] 1991	Poland	Sausages Other cured meat Table salt	Levels of frequency	1.5[3] 1.0[3] 1.6[2]	P trend $= 0.06$ N/S trend (1.2-2.3)
Ramón, *et al*[41] 1993	Spain	Smoked/pickled foods Salt intake	Quartiles of amount	3.7 2.1	(1.4-9.0) (1.2-7.1)
Nazario, *et al*[94] 1993	Puerto Rico	Salt intake	Quartiles of amount	6.7	(2.7-16.8)
Hassaon, *et al*[42] 1993	Sweden	Salted fish Smoked fish Sausages Bacon	Levels of frequency	0.8[4] 0.8[3] 0.9[3] 1.4[4]	(0.5-1.3) (0.5-1.2) (0.6-1.3) (0.9-2.2)
Cohort					
Hirohata[50] 1983	Japan	Salted fish Dried fish	Mean intake	Increase Increase	$P < 0.05$ $P < 0.05$

Continued...

Table 4. Continued

Nomura, *et al*[7] 1990	Hawaii, USA Japanese	Salted vegetables	3 levels of frequency	1.2	(0.8-1.7)
		Tsukudani		1.0	(0.4-2.6)
		Ham/bacon/sausages		1.3	(0.9-2.0)
		Table salt/soy sauce		1.0	(0.6-1.6)
Kneller, *et al*[9] 1991	USA	Salted fish	Levels of frequency	1.9[3]	(1.0-3.6)
		Bacon/side pork		1.4[4]	(0.6-3.1)
Kato, *et al*[10] 1992	Japan	Salted vegetables	3 levels of frequency	0.8	(0.4-1.5)

[a] RR = relative risk, for the highest versus lowest level. Numbers of categories are presented in brackets when differently categorized.
[b] CI = 95% confidence interval.
[c] N/S = not significant.
[d] Comparison of daily *cf* nondaily.

genesis induced experimentally in various organs,[73] and it was also shown that β-carotene or canthaxanthin inhibited the progression to carcinoma in the stomach of rats treated with a chemical carcinogen.[76]

Nitrite, nitrate, and *N*-nitroso compounds

Many *N*-nitroso compounds are known to be carcinogenic in animal experiments[54,55] and the possible formation of such compounds in the human stomach have raised a considerable concern regarding the role of nitrite or nitrate in the causation of human stomach cancer.[77,78] Nitrite reacts with amines, amides, and other proteins to form *N*-nitroso compounds. Nitrate itself is not a direct nitrosating agent, but is reduced to nitrite by many bacterial species harboring in the mouth and achlorhydric stomach. Nitrosation is an acid-catalyzed chemical reaction in the normoacidic stomach while it is catalyzed by intestinal bacteria in the achlorhydric stomach. It is unclear which way of nitrosation is more important in the intragastric formation of *N*-nitroso compounds. The major sources of nitrate and nitrite are vegetables and preserved meats, respectively. Drinking water is an additional source of nitrate intake, but nitrite intake via drinking water is usually negligible. In most circumstances, daily intake of nitrate is approximately 100-fold greater than that of nitrite, and thus nitrate is more relevant to the endogenous formation of *N*-nitroso compounds.[77]

Ecologic studies

As reviewed in detail elsewhere,[77,78] results from between-population studies in various countries are inconsistent regarding the association between nitrate exposure and stomach cancer risk. The earliest study in Britain reported an excess mortality from stomach cancer in the town of Worksop, where nitrate concentrations in drinking water had been the highest in any borough in the country.[79] In Columbia,[80] nitrate content in well water was higher in areas with high rates of stomach cancer than in low risk areas, and the use of well water was more frequent in the high risk areas. A strong geographic correlation was observed between the use of nitrate fertilizer and stomach cancer mortality in Chile.[81] However, such a positive correlation has not been reproduced in other studies.[82-84]

Case-control studies

A limited number of studies examined the association between dietary intake of nitrate and stomach cancer risk. Nitrate intake was associated negatively with risk significantly in Canada,[29] Spain,[59] and Sweden[60] and insignificantly in Germany[37] and Italy.[56] In these studies, vegetable intake was related consistently to a decreased risk of stomach cancer (Table 1). Nitrate intake is probably an index of vegetable intake, and the findings are not surprising. Four of these studies investigated the association with dietary nitrite intake with adjustment for total caloric intake or total food consumption. Two studies[29,56] observed a significant positive association of stomach cancer risk with nitrite intake, and the other two[59,60] found no measurable association. A reported association with nitrite intake is most likely to have reflected a positive association with preserved meats,[29,56] which are typical high-salt foods in Western countries, and does not necessarily support an etiologic role of nitrite.

The overall evidence from limited epidemiologic studies neither supports nor denies a hypothesis that nitrate intake may determine the risk of stomach cancer in humans. Because many factors appear to modify the intragastric nitrosation, and particularly because vegetables are a common source of intake of nitrate and micronutrients inhibiting the nitrosation, it seems difficult to detect any effect of nitrate intake in epidemiologic studies.[78]

Animal and mechanistic studies

If nitrate or nitrite intake is not a major determinant of stomach cancer risk, nitrosable substrates may be of

greater importance in the human gastric carcinogenesis. Specific foods in high-risk populations, such as fava beans in Columbia[85] and salted fish in Japan,[86] were shown to be mutagenic after *in vitro* nitrosation. Japanese salted fish, after nitrosation, also was reported to induce adenocarcinoma of the glandular stomach in rats.[87]

Salty foods and salt

Ecologic studies

Descriptive features of stroke and stomach cancer are similar with regard to worldwide distribution, secular trend, and social gradient, and it has been postulated that excessive salt intake is a common risk factor for stroke and stomach cancer.[88] While geographic variation in stomach cancer mortality in Japan is not correlated with *per capita* salt consumption estimated in the national nutrition survey,[89,90] two independent correlation studies[91,92] of selected areas in Japan noted an almost linear correlation between stomach cancer mortality and urinary salt excretion[91] or salt intake estimated from the consumption of salty foods.[92] In an ecologic study of 65 rural counties in China,[21] the consumption of salt-preserved vegetables is correlated positively with stomach cancer mortality ($r = 0.26$ in males and $r = 0.36$ in females).

Case-control studies

Many, but not all, case-control studies have found a positive association with intake of high salt foods such as salted fish, cured meat, and salted vegetables or the use of table salt, as summarized in Table 4.[23,25-29,31-39,41,42,57,93,94] Several studies quantitatively estimated total salt intake, and found a strong positive association with stomach cancer risk in Spain,[41] US,[57] and Puerto Rico,[94] but not in Canada.[29] Because high-starch diets may be associated positively with stomach cancer risk (see below), adjustment for total caloric intake or starchy food consumption is particularly important in evaluating a positive association with salt intake. An increased risk of stomach cancer associated with salty foods was independent of cereal and rice consumption in a Spanish study.[41] Similarly, a positive association with salty foods was noted in another Spanish study[38] allowing for total caloric intake. Since Graham *et al*[57] and Nazario *et al*[94] made no adjustment for either total caloric or carbohydrate intake, a notable increase in the risk associated with salt intake may have been overestimated in their studies.

In a study in Puerto Rico,[94] cases comprised those with intestinal type of stomach cancer, and the authors argued that salt intake was associated specifically with intestinal type of stomach cancer. Some other studies, however, have failed to find differential association for intestinal and diffuse types of stomach cancer regarding intake of salty foods.[25,39,46] Again, a study in Italy[47] noted a positive association with salted or dried fish for both cardiac and other gastric cancers.

The introduction of refrigerators has changed the method of preserving foods, and salting and smoking have become less popular in industrialized countries. Several case-control studies consistently have observed a decreased risk with the long-term use of the refrigerator,[29,35-37,57] even after allowance for socioeconomic status.[35,36,57] These findings indirectly support the salt hypothesis although refrigeration also may have increased the availability of fresh vegetables and fruit.

Cohort studies

Prospective data are scanty and less pronounced, but the findings are compatible with the assertion that intake of salty foods is associated with an increased risk (Table 4).[7,9,10,50] None of these studies adjusted for total caloric intake or the consumption of high-carbohydrate foods.

Animal and mechanistic studies

High salt concentration, rather than total salt intake, seems to be important as a cofactor in the causation of stomach cancer. Excessive salt intake induces superficial gastritis and atrophic gastritis, which are hypothesized to be initial lesions in human gastric carcinogenesis.[18] High salt intake was shown to have both co-initiating and promoting effects in the chemical carcinogenesis in the glandular stomach of rodents.[95,96] Intragastric high-salt concentrations lead to mucosal damage, thereby enhancing the contact of carcinogens to the epithelium. Salt-induced proliferative changes in the epithelium may pertain to the promoting effect in the gastric carcinogenesis.

High-starch diets

Ecologic studies

Cereal consumption was correlated moderately with between-country variation in stomach cancer mortality and incidence.[19] In China,[21] consumption indices of starchy foods such as potatoes, wheat, and millet were correlated moderately with stomach cancer mortality in 65 counties, but rice consumption showed a negative correlation. Rice consumption is little correlated with prefectural variation or declining trend in stomach cancer mortality in Japan.[6,22]

Case-control studies

Findings on high-starch diets are not as consistent as those for fresh vegetables and fruit or salty foods. Several studies found an increased risk in relation to high consumption of carbohydrates, starch, or cereals as a whole

in the US,[57] Canada,[29] Norway,[26] Belgium,[40] Italy,[56] Greece,[30] Spain,[41] and Israel[97] while some other studies failed to find such an association in the US,[28] Spain,[38] and Sweden.[60] Of individual high-starch foods, pasta was found to be a risk factor in Greece[30] and Italy.[32] Rice consumption was associated with an increased risk in Japanese in Hawaii,[25] but not necessarily so in Japan.[23,27,33] None of the main staple foods was associated materially with stomach cancer in China.[34] An association between high-starch foods and stomach cancer risk may be more difficult to show in Japan and China, where high-starch food consumption varies less at higher levels than in Western countries.

Cohort studies

A increased risk of stomach cancer was associated with high consumption of carbohydrates in the US[9] and with rice consumption in Japanese men in Hawaii.[7] Again, neither of two cohort studies in Japan[8,50] found a positive association between rice and stomach cancer.

Mechanisms and animal studies

Low-protein content has been suspected to be responsible for the positive association between high-starch diets and stomach cancer risk.[54] High-starch, low-protein diets may favor the acid-catalyzed nitrosation in the stomach because of poor buffering capacity of such diets. Low protein diets may decrease gastric mucous production and enhance carcinogen absorption. However, protein intake has never been related to a decreased risk in either case-control or cohort studies.[51,56-60] An inverse association with milk and other dairy products has been reported occasionally,[23,25,37] but was not reproducible in many epidemiologic studies. High-starch diets also may result in mechanical damage in the gastric mucosa.

Other dietary factors

Green tea

A possible anticarcinogenic effect of green tea has been a recent topic in cancer epidemiology. A protective association between green tea and stomach cancer was found in case-control studies in Japan[33] and China.[98] The most recent study in China[99] showed a clear dose-response relationship between green tea consumption and stomach cancer. Those who consumed four or more batches of green tea per day had an odds ratio of 0.54 compared with nondrinkers. As reviewed elsewhere,[100,101] polyphenol extracts of green tea and related compounds are known to inhibit tumorigenesis of various organs in experimental animals. A recent animal study[102] demonstrated that epigallocathechin, a major component of green tea polyphenols, inhibited chemical carcinogenesis in the glandular stomach in rats. Polyphenols in black tea are oxidated and polymerized in the process of fermentation, and it remains uncertain whether such compounds have the same anticarcinogenic effects as green tea polyphenols.[101] A recent case-control study in Sweden[42] noted that black tea consumption was associated with a substantial decrease in stomach cancer risk, while earlier case-control and cohort studies have failed consistently to find a protective association between black tea and stomach cancer.[100]

Chili pepper

Capsaicin, the pungent component of chili peppers, has been shown to be mutagenic and carcinogenic, and also to have a promoting effect in animal studies.[103,104] A case-control study in Mexico[105] initially reported that chili pepper consumption was associated with an increased risk of stomach cancer, especially of intestinal type.

Alcohol

An increased risk of stomach cancer was associated with heavy consumption of red wine in French men,[106] and with a habit of drinking vodka before breakfast in Poland.[31] Two cohort studies,[10,107] based on limited numbers of deaths from stomach cancer, also reported an increased risk with high alcohol consumption. The majority of case-control studies and larger cohort studies have found no measurable association between alcohol and stomach cancer, however.[7,8,108]

Summary and conclusions

Numerous case-control studies have shown a protective association with fresh vegetables and fruits although limited cohort studies have lent little evidence. Among possible protective components of vegetables and fruits are vitamins C and E, carotenoids, and selenium. Case-control studies are remarkably consistent in that dietary intakes of vitamin C and carotenoids are associated with a decreased risk. A limited number of cohort studies also have supported the protective effects of vitamin C and carotenoids. It is possible, however, that factors other than vitamin C and carotenoids also may contribute to lower risk of stomach cancer. Epidemiologic data are sparse and inconsistent as to protective effects of vitamin E and selenium. While experimental data suggest a possible etiologic role of nitrate intake in human gastric carcinogenesis, epidemiologic studies have not lent supportive evidence. It seems difficult to isolate a possible association between nitrate intake and stomach cancer in epidemiologic studies.

High salt intake has been associated with an increased risk in many case-control studies. Supportive, though limited, evidence also has been obtained from cohort

studies. Taken together with animal data, the overall evidence suggests that high salt intake is a risk factor for stomach cancer. Although quantitative data are not available, the worldwide decline in stomach cancer incidence could be ascribed at least partly to decreasing consumption of salty foods as well as increasing consumption of fresh vegetables and fruit. The findings from case-control and cohort studies are rather inconsistent as to whether high-starch diets confer an increased risk.

Epidemiologic evidence as to dietary hypothesis has been derived largely from case-control studies. Cohort studies based on quantitative dietary assessment and using biologic measurement of micronutrients will be useful for clarification of dietary hypothesis. Intervention trials on subjects with and without chronic atrophic gastritis are warranted to elucidate a specific protective effect of an individual micronutrient at different stages in human gastric carcinogenesis. Further research is needed regarding possible protective effects of green tea and garlic or related vegetables, as well as the association with chili pepper. It is of particular interest to examine the interaction of dietary factors and *H. pylori* infection in the causation of stomach cancer because the latter seems to play an important role at early steps in gastric carcinogenesis.

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