Nutrition and gastric cancer risk: an update

Chun Liu and Robert M Russell

Data from epidemiologic, experimental, and animal studies indicate that diet plays an important role in the etiology of gastric cancer. High intake of fresh fruits and vegetables, lycopene and lycopene-containing food products, and potentially vitamin C and selenium may reduce the risk for gastric cancer. Data also suggest that high intake of nitrosamines, processed meat products, salt and salted foods, and overweight and obesity are associated with increased risk for gastric cancer. However, current data provide little support for an association of β-carotene, vitamin E, and alcohol consumption with risk for gastric cancer.

INTRODUCTION

Gastric cancer is the fourth most frequent cancer and the second leading cause of cancer death worldwide. Gastric cancer is relatively uncommon in the United States, ranking 14th among both incident cancers and cancer deaths, with approximately 22,280 new cases and 11,430 deaths reported in 2006. The death rate from gastric cancer has gradually declined over the last several decades in the United States and worldwide, indicating that environmental factors (e.g., diet) play a critical role in the etiology of this malignancy. Mounting evidence indicates that gastric cardia (the part of the stomach nearest to the esophagus) and non-cardia (the middle or lower part of the stomach) cancer differ in etiology. The incidence of gastric cardia cancer has risen in the United States and in European countries, whereas the incidence of gastric non-cardia cancer has steadily decreased. The rising rate of obesity has been suggested to contribute to this increase in gastric cardia cancer.

FRUITS AND VEGETABLES

The association between intake of fruits and vegetables and risk for gastric cancer has been evaluated extensively in observational epidemiologic studies. The studies generally suggest an inverse association, particularly for raw and allium vegetables and citrus fruits. Meta-analyses have shown that the inverse association is stronger for fruits than for vegetables, but it was weaker in cohort studies than in case-control studies. In the 2003 report of the International Agency for Research on Cancer (IARC), the summary relative risks comparing high to low categories for fruits were 0.63 (95% confidence interval [CI] 0.58–0.69) from 37 case-control studies and 0.85 (95% CI 0.77–0.95) from 11 cohort studies. Regarding vegetables, the summary relative risks comparing high to low categories were 0.66 (95% CI 0.61–0.71) from 20 case-control studies and 0.94 (95% CI 0.84–1.06) from 5 cohort studies. Several case-control studies included in the IARC meta-analysis also showed that the association between intake of fruits and vegetables and gastric cancer risk was similar by gastric anatomic site. In the 2005 meta-analysis of cohort studies, the summary relative risks of gastric cancer were 0.82 (95% CI 0.73–0.93) for fruits and 0.88 (95% CI 0.69–1.13) for vegetables.

Recently, two large European cohort studies reported the results on fruit and vegetable consumption and gastric cancer risk by anatomic site. In the prospective analysis of the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study, among 29,133 male smokers high consumption of fruits was associated with a lower risk of gastric non-cardia cancer, but not with gastric cardia cancer. However, consumption of vegetables was...
not associated with risk for either gastric cardia or non-cardia cancer in the ATBC Cancer Prevention Study. The results from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, conducted among 521,457 men and women living in 10 European countries, showed no significant association of consumption of fresh fruits, total vegetables, or specific groups of vegetables with risk for gastric cancer regardless of anatomic site, although a non-significant inverse association was observed for citrus fruits or onion and garlic and risk for gastric cardia cancer only.

**ANTIOXIDANT NUTRIENTS**

Recent systemic reviews and meta-analyses of randomized trial data revealed that antioxidant supplements of β-carotene, vitamin A, and vitamin E, with the potential exception for selenium and vitamin C, had no significant effect on the incidence of gastrointestinal cancers; on the contrary, β-carotene, vitamin A, and vitamin E may be associated with increased mortality. To date, no randomized trials have evaluated the effect of lycopene, α-carotene, lutein/zeaxanthin, or β-cryptoxanthin on the prevention of gastric cancer.

**Carotenoids**

Carotenoids are lipid-soluble compounds that are rich in fruits and vegetables and responsible for the color of many fruits and vegetables. α-Carotene, β-carotene, lycopene, lutein/zeaxanthin, and β-cryptoxanthin are the most abundant carotenoids from the diet and in the circulation of humans. Several carotenoids (such as α-carotene, β-carotene, and β-cryptoxanthin) present in fruits and vegetables can be partially metabolized to retinol.

*Experimental studies.* Carotenoids (lycopen, lutein, and β-carotene) and retinoids have been shown to inhibit the incidence and growth of the chemically induced gastric tumors in laboratory animal studies. Experimental and animal studies suggest several potential mechanisms by which carotenoids may affect gastric carcinogenesis. Carotenoids can act as antioxidants to do the following: neutralize reactive oxygen species, thereby protecting DNA from oxidative damage; decrease cell proliferation and induce apoptosis; modify cell-cell communication; enhance host immunologic functions; and reduce *Helicobacter pylori* bacterial load and gastric inflammation by shifting the T-lymphocyte response from a predominant Th1-response dominated by γ-interferon to a Th1/Th2-response with γ-interferon and interleukin (IL)-4. In addition, in several human cross-sectional studies, plasma lycopene and other carotenoid concentrations have been inversely associated with inflammatory markers.

Using the ferret animal model, the effects of lycopene supplementation on cigarette-smoke-induced changes in protein levels of p53 tumor suppressor gene, p53 target genes (p21<sup>Waf1/Cip1</sup> and Bax-1), cell proliferation, and apoptosis in the gastric mucosa were examined. p21<sup>Waf1/Cip1</sup> (a CDK inhibitor) is a key component in the cell cycle arrest in G1, and Bax is a pro-apoptotic member of the Bcl-2 family. p21<sup>Waf1/Cip1</sup> and Bax-1 function as mediators to promote p53-dependent apoptosis. In that study, ferrets were assigned to cigarette smoke exposure or to no cigarette smoke exposure and to low-dose, or high-dose lycopene supplementation, or to no lycopene for nine weeks. Lycopene concentrations were significantly elevated in a dose-dependent manner in the gastric mucosa of ferrets supplemented with lycopene alone, but were markedly reduced in ferrets supplemented with lycopene and exposed to smoke. It was also found that total p53 and phosphorylated p53 levels were higher in ferrets exposed to smoke alone than in all other groups. However, smoke-elevated total p53 and phosphorylated p53 were markedly attenuated by both doses of lycopene. p21<sup>Waf1/Cip1</sup>, Bax-1, and cleaved caspase 3 (an index for apoptosis) were substantially decreased, whereas cell proliferation indices like cyclin D1 and proliferating cellular nuclear antigen (PCNA) were increased in ferrets exposed to smoke alone, while lycopene prevented smoke-induced changes in p21<sup>Waf1/Cip1</sup>, Bax-1, cleaved caspase 3, cyclin D1, and PCNA in a dose-dependent fashion. p53 phosphorylation, especially at serine 15, is an early cellular response to various genotoxic carcinogens and stresses that produce reactive oxygen species, and facilitates both the accumulation and functional activation of p53. Our data indicate that lycopene may prevent smoke exposure-induced changes in p53, p53 phosphorylation, p53 target genes, cell proliferation, and apoptosis in the gastric mucosa of ferrets, suggesting that lycopene may protect against the development of gastric cancer by modulating p53-dependent cell cycle control and apoptosis.
Table 1  Epidemiologic studies of lycopene and lycopene products and gastric cancer risk.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Outcome</th>
<th>No. of cases</th>
<th>Exposure</th>
<th>Comparison</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective studies</td>
<td></td>
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<tr>
<td>Yuan et al. (2004)</td>
<td>Shanghai, China</td>
<td>GC</td>
<td>191</td>
<td>Serum lycopene</td>
<td>Quartile 4 vs. 1</td>
<td>0.63 (0.34–1.15)</td>
</tr>
<tr>
<td>Jenab et al. (2006)</td>
<td>Europe</td>
<td>GC</td>
<td>244</td>
<td>Plasma lycopene</td>
<td>Quartile 4 vs. 1</td>
<td>0.63 (0.36–1.09)</td>
</tr>
<tr>
<td>Botterweck et al. (2000)</td>
<td>Netherlands</td>
<td>GC</td>
<td>282</td>
<td>Dietary lycopene</td>
<td>Quintile 5 vs. 1</td>
<td>1.0 (0.7–1.5)</td>
</tr>
<tr>
<td>Nouraei et al. (2005)</td>
<td>Finland</td>
<td>GCC</td>
<td>57 (M)</td>
<td>Dietary lycopene</td>
<td>Quartile 4 vs. 1</td>
<td>0.97 (0.41–2.34)</td>
</tr>
<tr>
<td>Larsson et al. (2007)</td>
<td>Sweden</td>
<td>GC</td>
<td>139</td>
<td>Dietary lycopene</td>
<td>Quartile 4 vs. 1</td>
<td>0.62 (0.37–1.03)</td>
</tr>
<tr>
<td>Case-control studies</td>
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<tr>
<td>Harrison et al. (1997)</td>
<td>New York</td>
<td>GC, intestinal</td>
<td>60</td>
<td>Dietary lycopene</td>
<td>One S.D. increment</td>
<td>0.7 (0.4–1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GC, diffuse</td>
<td>31</td>
<td></td>
<td>One S.D. increment</td>
<td>0.8 (0.5–1.4)</td>
</tr>
<tr>
<td>Garcia-Closas et al. (1999)</td>
<td>Spain</td>
<td>GC</td>
<td>354</td>
<td>Dietary lycopene</td>
<td>Quartile 4 vs. 1</td>
<td>1.55 (0.91–2.64)</td>
</tr>
<tr>
<td>De Stefani et al. (2000)</td>
<td>Uruguay</td>
<td>GC</td>
<td>120</td>
<td>Dietary lycopene</td>
<td>Tertile 3 vs. 1</td>
<td>0.37 (0.19–0.73)</td>
</tr>
<tr>
<td>Lisowski et al. (2004)</td>
<td>Poland</td>
<td>GC</td>
<td>274</td>
<td>Dietary lycopene</td>
<td>Quartile 4 vs. 1</td>
<td>1.19 (0.77–1.82)</td>
</tr>
<tr>
<td>Haenszel et al. (1972)</td>
<td>Hawaiian</td>
<td>GC</td>
<td>220</td>
<td>Tomato intake</td>
<td>≥11 vs. &lt;4/month</td>
<td>0.39, p &lt; 0.05, all; 0.31, p &lt; 0.05,</td>
</tr>
<tr>
<td>Tajima and Tominaga (1985)</td>
<td>Japan</td>
<td>GC</td>
<td>93</td>
<td>Tomato intake</td>
<td>≥4 vs. ≤1/week</td>
<td></td>
</tr>
<tr>
<td>Correa et al. (1985)</td>
<td>Louisiana</td>
<td>GC</td>
<td>194</td>
<td>Tomato intake</td>
<td>&gt; vs. ≤ median</td>
<td>0.82 (0.53–1.28), whites</td>
</tr>
<tr>
<td>La Vecchia et al. (1987)</td>
<td>Italy</td>
<td>GC</td>
<td>206</td>
<td>Tomato intake</td>
<td>&gt; vs. ≤ median</td>
<td>0.56 (0.34–0.90), blacks</td>
</tr>
<tr>
<td>Buiatti et al. (1989)</td>
<td>Italy</td>
<td>GC</td>
<td>1,016</td>
<td>Tomato intake</td>
<td>Tertile 3 vs. 1</td>
<td>0.69, NS</td>
</tr>
<tr>
<td>Graham et al. (1990)</td>
<td>New York</td>
<td>GC</td>
<td>186 (M)</td>
<td>Tomato intake</td>
<td>Tertile 3 vs. 1</td>
<td>0.70, p for trend &lt;0.001</td>
</tr>
<tr>
<td>González et al. (1991)</td>
<td>Spain</td>
<td>GC</td>
<td>354</td>
<td>Tomato intake</td>
<td>Tertile 3 vs. 1</td>
<td>Reduced risk, p &lt; 0.05 Reduced risk, NS</td>
</tr>
<tr>
<td>Boeing et al. (1991)</td>
<td>Poland</td>
<td>GC</td>
<td>741</td>
<td>Tomato intake</td>
<td>Quartile 4 vs. 1</td>
<td>0.9 (0.5–1.5)</td>
</tr>
<tr>
<td>Tuyns et al. (1992)</td>
<td>Belgium</td>
<td>GC</td>
<td>449</td>
<td>Tomato intake</td>
<td>Tertile 3 vs. 1</td>
<td>0.77, p for trend &lt;0.05</td>
</tr>
<tr>
<td>Hansson et al. (1993)</td>
<td>Sweden</td>
<td>GC</td>
<td>338</td>
<td>Tomato intake, adolescence</td>
<td>&gt;0 vs. 0 g/week</td>
<td>0.12, NS</td>
</tr>
<tr>
<td>Franceschi et al. (1994)</td>
<td>Italy</td>
<td>GC</td>
<td>723</td>
<td>Tomato intake</td>
<td>＞20 years early</td>
<td>0.36 (0.23–0.58)</td>
</tr>
<tr>
<td>Ekström et al. (2000)</td>
<td>Sweden</td>
<td>GCC</td>
<td>74</td>
<td>Tomato intake</td>
<td>Quartile 4 vs. 1</td>
<td>0.12, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GNCC</td>
<td>406</td>
<td>Tomato intake</td>
<td>≥4/week vs. ≤1–3/month</td>
<td>0.72 (0.47–1.11)</td>
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<td></td>
<td>0.43 (0.33–0.55)</td>
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<td></td>
<td>0.6 (0.3–1.1)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8 (0.6–1.2)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; GC, gastric cancer; GCC, gastric cardia cancer; GNCC, gastric non-cardia cancer; NS, not significant; M, male; F, female.
β-carotene with other antioxidants on gastric cancer prevention. Daily β-carotene supplementation (30 mg) for six years among individuals with multifocal nonmetaplastic atrophy and/or intestinal metaplasia (premalignant lesions) significantly increased the rates of regression in the Columbia trial. In the General Population Trial of Linxian, China, among 29,584 high-risk individuals with suboptimal nutritional status, randomized daily treatment for 5.25 years with supplements containing β-carotene (15 mg), α-tocopherol (30 mg), and selenium from yeast (50 µg) resulted in a non-significant reduction in both the incidence of and mortality from gastric cardia and non-cardia cancer. Two randomized trials in well-nourished Western populations, however, found no beneficial effect of β-carotene for reducing the risk for gastric cancer. Although the number of gastric cancers was small in one of these studies, the results showed that 50 mg of β-carotene supplementation every other day for 12 years did not affect the risk for gastric cancer among 22,071 apparently healthy US male physicians. In the ATBC Cancer Prevention Study, randomized daily treatment with β-carotene (20 mg) or with combined β-carotene (20 mg) and α-tocopherol (50 mg) for five to eight years led to a non-significant, increased risk for gastric cancer among 29,133 Finnish male smokers; however, it had no influence on the occurrence of neoplastic changes of the stomach in male smokers with atrophic gastritis.

Vitamin C

Experimental studies. Vitamin C (ascorbic acid) is a water-soluble antioxidant that is abundant in fruits and vegetables and can regenerate vitamin E from its oxidized form. The effect of vitamin C on experimentally induced gastric cancer in laboratory rodents is conflicting, with studies showing an inhibitory effect, no effect, or a promoting effect. A few studies reported a promoting effect of vitamin C on forestomach carcinogenesis when it was coadministered with sodium nitrite following pretreatment with chemical carcinogens, whereas vitamin C itself had no influence on forestomach or glandular stomach carcinogenesis. Data from experimental and animal studies indicate several potential mechanisms by which vitamin C may affect gastric carcinogenesis, including the following: vitamin C reduces gastric mucosal oxidative stress and DNA damage and gastric inflammation by scavenging reactive oxygen species; it inhibits gastric nitrosation reaction for the formation of N-nitroso compounds by reducing nitrous acid to nitric oxide and producing dehydroascorbic acid in the stomach; it enhances host immunologic functions; it has a direct effect on H. pylori growth and virulence; and it inhibits gastric cell proliferation and induces apoptosis.

Observational epidemiologic studies and randomized trials. Case-control studies have consistently reported an inverse association between vitamin C and gastric cancer risk. Most of the prospective cohort studies have also shown an inverse association. In the Basel Study, serum vitamin C levels were inversely associated with mortality from gastric cancer. In the EPIC cohort, plasma vitamin C levels were associated with reduced risk for gastric cancer, and this inverse association was similar according to anatomic site (cardia vs. non-cardia), histologic subtype (diffuse vs. intestinal), or H. pylori infection. Use of vitamin C supplements was also associated with reduced mortality from gastric cancer in the American Cancer Society Cancer Prevention Study II cohort. In the cohort analysis of the ATBC Cancer Prevention Study, high vitamin C intake was associated with reduced risk for gastric non-cardia cancer but not for gastric cardia cancer. However, the Netherlands Cohort Study found no association between vitamin C intake and risk for gastric cancer.

The results from several randomized trials that have assessed the efficacy of vitamin C in the prevention of gastric cancer are not entirely consistent (Table 2). One randomized trial in Japan among individuals with chronic gastritis reported that vitamin C slowed the progression of gastric mucosal atrophy, a precancerous lesion of gastric cancer. In that trial, daily treatment with 50 mg or 500 mg of vitamin C for five years significantly reduced the ratio of serum pepsinogen I/II, a marker of gastric atrophy. In an Italian trial among patients with intestinal metaplasia (premalignant lesions) on the gastric mucosa following H. pylori eradication, vitamin C supplementation (500 mg/day) for six months significantly increased the rate of regression of intestinal metaplasia. In the Columbia trial, individuals with multifocal nonmetaplastic atrophy and/or intestinal metaplasia (premalignant lesions) assigned to vitamin C supplements (1 g twice a day) also had significantly increased rates of regression over six years of treatment. However, supplementation with combined vitamin C (250 mg), vitamin E (100 IU), and selenium from yeast (37.5 µg) twice daily for 7.3 years did not lower the prevalence of precancerous gastric lesions and the incidence of gastric cancers in the Linqu trial in China. Randomized daily treatment with combined vitamin C (120 mg) and molybdenum supplements for 5.25 years also had no significant effect on both incidence and mortality from gastric cardia and non-cardia cancer in the General Population Trial of Linxian, China.

In human studies, treatment with high-dose vitamin C (5 g daily for 4 weeks) eradicated H. pylori infection. Vitamin C supplementation (1 g twice daily for 4–12 months) reduced the formation of nitrotyrosine, a nitrating product, among patients with H. pylori non-atrophic
Table 2  Randomized trials of vitamin C and gastric cancer risk.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Population</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>No. of cases</th>
<th>Intervention</th>
<th>Relative risk (95% CI) or p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sasazuki et al.</td>
<td>Japan</td>
<td>439 chronic gastritis participants</td>
<td>Reduction in serum pepsinogen I/II (a marker of gastric atrophy (precancerous lesions)</td>
<td>5 years</td>
<td></td>
<td>Vitamin C (50 mg) vs. placebo</td>
<td>0.0001</td>
</tr>
<tr>
<td>Zullo et al.</td>
<td>Italy</td>
<td>65 patients with intestinal metaplasia on the gastric mucosa following H. pylori eradication</td>
<td>Regression rate from intestinal metaplasia (premalignant lesions)</td>
<td>6 months</td>
<td></td>
<td>Vitamin C (500 mg) vs. placebo</td>
<td>0.01</td>
</tr>
<tr>
<td>Correa et al.</td>
<td></td>
<td>976 patients with multifocal nonmetaplastic atrophy and/or intestinal metaplasia</td>
<td>Regression rate from multifocal nonmetaplastic atrophy (premalignant lesions)</td>
<td>6 years</td>
<td></td>
<td>Vitamin C (1000 mg twice a day) vs. placebo</td>
<td>5.0 (1.7-14.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regression rate from intestinal metaplasia (premalignant lesions)</td>
<td>6 years</td>
<td></td>
<td>Vitamin C (1000 mg twice a day) vs. placebo</td>
<td>3.3 (1.1-9.5)</td>
</tr>
<tr>
<td>Blot et al.</td>
<td>Linxian, China</td>
<td>29,584 participants</td>
<td>GC</td>
<td>5.25 years</td>
<td>539</td>
<td>Combined vitamin C (120 mg)/molybdenum (30 μg) vs. placebo</td>
<td>1.10 (0.92-1.30)</td>
</tr>
<tr>
<td>Blot et al.</td>
<td>Linxian, China</td>
<td>29,584 participants</td>
<td>GCC</td>
<td>5.25 years</td>
<td>435</td>
<td>Combined vitamin C (120 mg)/molybdenum (30 μg) vs. placebo</td>
<td>1.07 (0.90-1.29)</td>
</tr>
<tr>
<td>Blot et al.</td>
<td>Linxian, China</td>
<td>29,584 participants</td>
<td>GC*</td>
<td>5.25 years</td>
<td>331</td>
<td>Combined vitamin C (120 mg)/molybdenum (30 μg) vs. placebo</td>
<td>1.09 (0.88-1.36)</td>
</tr>
<tr>
<td>Blot et al.</td>
<td>Linxian, China</td>
<td>29,584 participants</td>
<td>GCC*</td>
<td>5.25 years</td>
<td>253</td>
<td>Combined vitamin C (120 mg)/molybdenum (30 μg) vs. placebo</td>
<td>1.07 (0.84-1.37)</td>
</tr>
<tr>
<td>You et al.</td>
<td>Linqu, China</td>
<td>3365 participants</td>
<td>GC or GC only</td>
<td></td>
<td>2172 in 1999</td>
<td>Combined vitamin C (50 mg)/vitamin E (100 IU)/Se (37.5 μg) vs. placebo</td>
<td>1.32 (1.12-1.57) in 1999</td>
</tr>
<tr>
<td>You et al.</td>
<td>Linqu, China</td>
<td>3365 participants</td>
<td>Severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or GC</td>
<td></td>
<td>1945 in 2003</td>
<td>Combined vitamin C (250 mg)/vitamin E (100 IU)/Se (37.5 μg) vs. placebo</td>
<td>1.14 (0.96-1.37) in 2003</td>
</tr>
<tr>
<td>You et al.</td>
<td>Linqu, China</td>
<td>3365 participants</td>
<td>Dysplasia or GC</td>
<td>7.3 years</td>
<td>434 in 1999</td>
<td>Combined vitamin C (250 mg)/vitamin E (100 IU)/Se (37.5 μg) vs. placebo</td>
<td>1.10 (0.89-1.37) in 1999</td>
</tr>
<tr>
<td>You et al.</td>
<td>Linqu, China</td>
<td>3365 participants</td>
<td>GC only</td>
<td>7.3 years</td>
<td>58</td>
<td>Combined vitamin C (250 mg)/vitamin E (100 IU)/Se (37.5 μg) vs. placebo</td>
<td>1.03 (0.87-1.23) in 2003</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Se, selenium; GC, gastric cancer; GCC, gastric cardia cancer; GNCC, gastric non-cardia cancer.

* Death from GC, or GCC and GNCC.
gastritis. However, supplementation with combined vitamin C (200 mg) and vitamin E (50 mg) twice daily for four weeks failed to decrease reactive oxygen species and lipid peroxidation in the gastric mucosa of individuals with *H. pylori* gastritis.

**Vitamin E**

*Experimental studies.* Vitamin E (tocopherol) is a potent lipid-soluble antioxidant. In animal studies, vitamin E demonstrated the following abilities: reduce gastric oxidative stress and mucosal cell membranes from lipid peroxidation, inhibit nitration, and reduce the chemically induced gastric tumors, specifically in combination with other antioxidants, in some studies, but not in others. Vitamin E was ineffective in reducing gastric inflammation and premalignant lesions in Mongolian gerbils. In a human study of individuals with *H. pylori* gastritis, vitamin E (50 mg) combined with vitamin C (200 mg) twice daily for four weeks did not decrease reactive oxygen species and lipid peroxidation in gastric mucosa.

*Observational epidemiologic studies and randomized trials.* The results from observational epidemiologic studies have been mixed. High serum α-tocopherol levels were associated with reduced risk for gastric cancer in a Finnish cohort and mortality from gastric cancer in the Basel Study cohort. Plasma α-tocopherol, but not γ-tocopherol, was inversely associated with risk for gastric cancer in the EPIC cohort. However, in the Shanghai cohort study, serum levels of α-tocopherol and γ-tocopherol were not associated with risk for gastric cancer.

High vitamin E intake also was not associated with gastric cancer risk in the Netherlands Cohort Study. In addition, use of vitamin E supplements had no association with mortality from gastric cancer in the Cancer Prevention Study II cohort. In the cohort analysis of the ATBC Cancer Prevention Study, the association appeared to differ according to anatomic site—high intakes of α-tocopherol and γ-tocopherol were associated with increased risk for gastric cardia cancer but reduced risk for gastric non-cardia cancer. In the same study, elevated serum levels of α-tocopherol were associated with increased risk for gastric cardia cancer but had no association with risk for gastric non-cardia cancer.

Several randomized trials have evaluated vitamin E as a single agent or in combination with other antioxidants in the primary or secondary prevention of gastric cancer. The results from these trials provide little evidence that vitamin E reduces risk for gastric cancer and may even suggest an increased risk in men. In the General Population Trial of Linxian, China, randomized daily treatment for 5.25 years with supplements containing β-carotene (15 mg), vitamin E (30 mg), and selenium from yeast (50 μg) among poorly nourished populations resulted in a non-significant reduction in both the incidence of and mortality from gastric cardia and non-cardia cancer. In the Women's Health Study, randomized treatment with 600 IU of α-tocopherol every other day for ten years did not lower the risk for gastric cancer in 39,876 apparently healthy US women. In the ATBC Cancer Prevention Study, randomized daily treatment with 50 mg of α-tocopherol or with a combination of 20 mg of β-carotene and 50 mg of α-tocopherol over five to eight years resulted in a non-significant, increased risk for gastric cancer among Finnish male smokers. Two trials that have evaluated the effect of vitamin E on premalignant lesions also yielded mixed results. In a Russian trial of intestinal metaplasia patients, daily vitamin E supplementation (400 IU) for one year increased rates of regression. However, supplementation with combined vitamin E (100 IU), vitamin C (250 mg), and selenium from yeast (37.5 μg) twice daily for 7.3 years did not reduce the prevalence of precancerous gastric lesions and the incidence of gastric cancers in the Linqu trial in China.

**Selenium**

Selenium, an essential trace element for humans, is a component of 25 selenoproteins like glutathione peroxidases (GPx). The biologic effects of selenium occur mainly through the function of selenoproteins, which are involved in diverse biologic pathways, including the following: antioxidant defense, which can reduce oxidative stress and DNA damage; induction of phase II conjugating enzymes for detoxification of carcinogens and reduction of DNA adduct formation; inhibition of cell proliferation and promotion of DNA repair and apoptosis through p53 tumor suppressor gene; inactivation of protein kinase C (a receptor that is critical for tumor promotion); maintenance of normal DNA methylation; generation of active thyroid hormone; and enhancement of immune function, fertility, and muscle movement and function. Some of these health effects of selenium are not entirely due to its enzymatic functions. Limited animal studies reported mixed results on the effect of selenium on the chemically induced gastric tumors.

**Observational epidemiologic studies and randomized trials.** Data from human epidemiologic studies and one clinical trial suggest there is an important inverse association between selenium and gastric cancer risk, and the effect appears to be strongest in individuals with low selenium status (Table 3). High toenail selenium levels were associated with a non-significant, reduced risk of gastric cancer in the Netherlands Cohort Study. Elevated serum
Table 3  Epidemiologic studies and randomized trials of selenium and gastric cancer risk.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Outcome</th>
<th>No. of cases</th>
<th>Exposure</th>
<th>Comparison</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nomura et al. (1987)</td>
<td>Hawaii Japan</td>
<td>GC</td>
<td>66</td>
<td>Serum Se</td>
<td>Quintile 1 vs. 5</td>
<td>0.9, NS</td>
</tr>
<tr>
<td>Knekt et al. (1990)</td>
<td>Finland</td>
<td>GC</td>
<td>58 (M)</td>
<td>Serum Se</td>
<td>Quintile 5 vs. 1</td>
<td>0.26, p &lt; 0.01</td>
</tr>
<tr>
<td>Mark et al. (2000)</td>
<td>Linxian, China</td>
<td>GCC</td>
<td>402</td>
<td>Serum Se</td>
<td>Quartile 4 vs. 1</td>
<td>0.47 (0.33–0.65)</td>
</tr>
<tr>
<td>Wei et al. (2004)</td>
<td>Linxian, China</td>
<td>GCC*</td>
<td>36</td>
<td>Serum Se</td>
<td>Quartile 4 vs. 1</td>
<td>1.07 (0.55–2.08)</td>
</tr>
<tr>
<td>Van den Brandt et al. (1993)</td>
<td>The Netherlands</td>
<td>GC</td>
<td>92</td>
<td>Toenail Se</td>
<td>Quartile 4 vs. 1</td>
<td>0.31 (0.11–0.87)</td>
</tr>
<tr>
<td>Case-control studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Quintile 5 vs. 1</td>
<td>1.64 (0.49–5.48)</td>
</tr>
<tr>
<td>Kabuto et al. (1994)</td>
<td>Japan</td>
<td>GC</td>
<td>202</td>
<td>Serum Se</td>
<td>Quartile 1 vs. 4</td>
<td>1.0 (0.5–1.9)</td>
</tr>
<tr>
<td>Blot et al. (1993)</td>
<td>Linxian, China</td>
<td>GC</td>
<td>539</td>
<td>Combined β-carotene (15 mg)/vitamin E (30 mg)/Se (50 µg)</td>
<td>Treatment vs. placebo</td>
<td>0.84 (0.71–1.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GCC</td>
<td>435</td>
<td>Combined β-carotene (15 mg)/vitamin E (30 mg)/Se (50 µg)</td>
<td>Treatment vs. placebo</td>
<td>0.85 (0.70–1.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GNCC</td>
<td>104</td>
<td>Combined β-carotene (15 mg)/vitamin E (30 mg)/Se (50 µg)</td>
<td>Treatment vs. placebo</td>
<td>0.82 (0.56–1.20)</td>
</tr>
<tr>
<td>Blot et al. (1993)</td>
<td>Linxian, China</td>
<td>GC*</td>
<td>331</td>
<td>Combined β-carotene (15 mg)/vitamin E (30 mg)/Se (50 µg)</td>
<td>Treatment vs. placebo</td>
<td>0.79 (0.64–0.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GCC*</td>
<td>253</td>
<td>Combined β-carotene (15 mg)/vitamin E (30 mg)/Se (50 µg)</td>
<td>Treatment vs. placebo</td>
<td>0.82 (0.64–1.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GNCC*</td>
<td>78</td>
<td>Combined β-carotene (15 mg)/vitamin E (30 mg)/Se (50 µg)</td>
<td>Treatment vs. placebo</td>
<td>0.72 (0.46–1.14)</td>
</tr>
<tr>
<td>You et al. (2006)</td>
<td>Linqu, China</td>
<td>Dysplasia or GC</td>
<td>434 in 1999</td>
<td>Combined vitamin C (250 mg)/vitamin E (100 IU)/Se (37.5 µg)</td>
<td>Treatment vs. placebo</td>
<td>1.10 (0.89–1.37) in 1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysplasia or GC</td>
<td>921 in 2003</td>
<td>Combined vitamin C (250 mg)/vitamin E (100 IU)/Se (37.5 µg)</td>
<td>Treatment vs. placebo</td>
<td>1.03 (0.87–1.23) in 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GC only</td>
<td>58</td>
<td>Combined vitamin C (250 mg)/vitamin E (100 IU)/Se (37.5 µg)</td>
<td>Treatment vs. placebo</td>
<td>1.03 (0.61–1.73)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Se, selenium; GC, gastric cancer; GCC, gastric cardia cancer; GNCC, gastric non-cardia cancer; M, male; F, female.

* Death from GCC and GNCC.
selenium levels were also associated with reduced gastric cancer risk in a Finnish cohort, a population with low selenium intake, but not in a cohort of Japanese Americans in Hawaii or in a case-control study in Japan, where populations have relatively adequate selenium status, randomized daily treatment for 5.25 years with supplements containing β-carotene (15 mg), vitamin E (30 mg), and selenium from yeast (50 μg) led to a non-significant reduction in both the incidence of and mortality from gastric cardia and non-cardia cancer. In the prospective analysis of the General Population Trial of Linxian, China, that included populations with poor selenium status, randomized daily treatment for 5.25 years with supplements containing β-carotene (15 mg), vitamin E (30 mg), and selenium from yeast (50 μg) led to a non-significant reduction in both the incidence of and mortality from gastric cardia and non-cardia cancer. In the prospective analysis of the General Population Trial of Linxian, China, baseline serum selenium levels were highly and significantly associated with decreased incidence and mortality of gastric cardia cancer but not with non-cardia cancer. For gastric cancer incidence, the relative risks comparing the top with the bottom quartiles of serum selenium were 0.47 (95% CI 0.33–0.65) for gastric cardia cancer and 1.07 (95% CI 0.55–2.08) for non-cardia cancer. The corresponding relative risks for mortality were 0.31 (95% CI 0.11–0.87) for gastric cardia cancer and 1.64 (95 CI 0.49–5.48) for gastric non-cardia cancer. However, supplementation with combined vitamin C (250 mg), vitamin E (100 IU), and selenium from yeast (37.5 μg) twice daily for 7.3 years did not reduce the prevalence of precancerous gastric lesions and the incidence of gastric cancers in the Linqu trial in China.

Currently, there are two ongoing randomized trials that test the efficacy of selenium as a single agent on cancer incidence, namely the Selenium and Vitamin E Cancer Prevention Trial (SELECT) and the Prevention of Cancer by Intervention with Selenium (PRECISE) trial. The SELECT trial is examining the effect of selenium (200 μg/day from l-selenomethionine) and/or vitamin E (400 IU/day of all rac alpha-tocopheryl acetate) supplementation for a minimum of seven years (maximum of 12 years) on prostate cancer incidence in non-African American men aged 55 years or older and African American men aged 50 years or older. The PRECISE trial is designed to examine the effect of selenium on the incidence of cancer in the United Kingdom, Sweden, and Denmark, three countries with low selenium status. The results from these two randomized trials will provide important answers to questions about the role of selenium in the primary prevention of cancer.

Alcohol

Data from both experimental and epidemiologic studies provide little support for a harmful effect of alcohol on the development of gastric cancer.

Experimental studies. Animal studies on alcohol and gastric cancer are inconclusive. In experimental studies in rodents, 10% ethanol administered in drinking water did not promote the development of gastric tumors induced by N-methyl-N′-nitro-N-nitrosoguanidine (MNNG), a known gastric carcinogen. In addition, when wine or 11% ethanol was coadministered with MNNG in rats, wine or 11% ethanol was found to inhibit the MNNG-induced gastroduodenal carcinoma. However, an early study reported that the intraperitoneal injection of 20% ethanol in 0.9% sodium chloride increased the incidence and number of the MNNG-induced gastric cancers of glandular stomach in rats. Because ethanol and sodium chloride were given together, it is difficult to infer that the increased risk was attributable to ethanol or to sodium chloride, which have been shown to increase the incidence of MNNG-induced gastric tumors in rats.

Observational epidemiologic studies. The relationship between alcohol consumption and gastric cancer risk remains controversial. An early meta-analysis of 14 case-control studies and two cohort studies reported that alcohol consumption was associated with a modest increase in risk for gastric cancer; the summary relative risk for an increase of 25 g/day of alcohol was 1.07 (95% CI 1.04–1.10). However, recent data from four large prospective cohort studies and a prospective analysis of data from an automated database provide little support for the association between total alcohol consumption and gastric cancer risk. Data from the Norwegian cohort suggest that alcohol may interact with smoking to increase gastric cancer risk. In that study, smoking doubled the risk for gastric cancer, and alcohol consumption had no significant association with the risk, but combined high exposure to cigarettes (>20/day) and alcohol (>5 occasions/14 days) increased the risk for gastric non-cardia cancer 4.9-fold (95% CI 1.90–12.62) in comparison with nonusers of both cigarettes and alcohol. Findings have also been mixed regarding the relation of alcoholic beverage type to gastric cancer risk.

Salt and salted foods

Experimental studies. In laboratory rodents, numerous studies have shown that high-salt diets (2.5–10% NaCl) enhance chemically induced gastric tumors. A high concentration of salt in the stomach does the following: induces gastric inflammation; damages the mucosal protective layer; increases DNA synthesis and cell proliferation; and alters the mucous microenvironment in a dose-dependent fashion. The gastric mucosal damage and increased cell proliferation might increase carcinogenesis and the risk for gastric cancer. In mice, the mucosal damage caused by a high-salt diet enhances persistent
H. pylori infection. Studies in Mongolian gerbils show that a high-salt diet also acts synergistically with H. pylori infection to promote the development of gastric tumors induced by N-methyl-N-nitrosourea (MNU). However, MNU initiation was required for tumor induction, as no tumors were found in gerbils without MNU treatment in spite of their H. pylori and/or high-salt diet treatments. A study using outbred Mongolian gerbils found that atrophic gastritis and intestinal metaplasia developed both in animals infected with H. pylori and in uninfected animals fed with a 2.5% salt diet, but no dysplasia or tumor development was observed. No synergism was found between H. pylori infection and a 7.5% salt diet in relation to gastric tumors in INS-GAS” and wild-type B6129 mouse models.” These data suggest that a high-salt diet may not be sufficient to initiate gastric carcinogenesis by itself and that a high-salt diet may not have a co-promoting effect with H. pylori infection on gastric cancer.

Observational epidemiologic studies. The association between salt and salted foods and gastric cancer risk has been evaluated in more than 40 epidemiologic case-control studies and several prospective cohort studies. Most case-control studies have found a positive association between intake of salt and high-salt foods, such as salted vegetables, fish, and cured meat products, and risk of gastric cancer. A high-salt diet and H. pylori infection have also been found to act synergistically to increase the risk for gastric cancer in a Korean case-control study. Prospective data are limited and less consistent. In a US cohort, salted fish intake was associated with increased mortality from gastric cancer among men. A Japanese cohort study also observed a non-significant, increased rate of mortality from gastric cancer associated with high intake of pickled foods and traditional soups. The Netherlands Cohort Study reported that intakes of salt and several types of cured meat were weakly but positively associated with gastric cancer risk, while salt added to the hot meal or to soup during cooking or the use of table salt had no association. In another large, prospective, cohort study in Japan, high salt intake was significantly associated with increased risk for gastric cancer in men, but not in women, and highly salted foods, such as salted fish roe and salted fish preserves, were strongly associated with increased risk in both men and women. However, a prospective study of Japanese men in Hawaii reported no association with intake of table salt/shoyu.

High-salt foods such as processed meat products and salted fish are also important sources of nitrates and/or nitrosamines. A recent evaluation from a joint World Health Organization/Food and Agriculture Organization Expert Consultation concluded that salt-preserved foods and salt are probable risk factors that increase the risk of gastric cancer.

Nitrate, nitrite, and nitrosamines

There are two sources of nitrosamines that humans are exposed to, namely preformed exogenous nitrosamines and nitrosamines produced endogenously from nitrate and nitrite. Preformed nitrosamines are present mainly in nitrite-cured meat and fish and other foods, smoked, pickled, and salty preserved foods, and alcoholic beverages (beer and whisky). Nitrate, a natural compound, is present in vegetables and drinking water and is used as a food additive in cheese and cured meat. N-nitroso compounds are also found in tobacco products, drugs, and industrial materials. Dietary nitrate can be reduced to nitrite by oral bacteria and then to N-nitroso compounds (e.g. nitrosamines) by acid-catalyzed and bacterial nitrosation in the stomach through the reaction with compounds such as amines, amidines, and amino acids. The in vivo formation of nitrosamines can also occur via nitric oxide (NO) formation during inflammation.

N-nitroso compounds have been found to be carcinogenic in animal studies. Two nitrosamines (N-nitrosodiethylamine and N-nitrosodimethylamine) are classified as probably carcinogenic to humans (group 2A) by the IARC. Epidemiologic studies suggest a positive association between nitrosamines and gastric cancer risk, but the data are still inconclusive. Most epidemiologic investigations on nitrosamine and related food intake and gastric cancer risk have been case-control investigations, which support a positive association of nitrite, nitrosamine, processed meat and fish, preserved vegetables, and smoked food intake with risk for gastric cancer.

Only a few prospective cohorts have evaluated the association between intake of nitrate, nitrite, or nitrosamine and risk of gastric cancer, and the findings are not entirely consistent. In the Netherlands Cohort Study, intake of nitrate was not associated with gastric cancer risk whereas intake of nitrite was non-significantly but positively associated with the risk. There was no association between intakes of nitrate, nitrite, or N-nitrosodimethylamine and risk of gastric cancer in a Finnish cohort study. The EPIC cohort study found no association between dietary intake of N-nitrosodimethylamine and gastric cancer risk, but endogenous formation of N-nitroso compounds was significantly associated with risk for gastric non-cardia cancer (relative risk 1.42, 95% CI 1.14–1.78 for an increase of 40 μg/day) but not with gastric cardia cancer (relative risk 0.96, 95% CI 0.69–1.33). Data from the EPIC cohort also suggested a possible interaction of...
endogenous formation of nitroso compounds with \textit{H. pylori} infection or plasma vitamin C levels; the positive association between endogenous formation of nitroso compounds and risk for gastric non-cardia cancer was present only in those who were infected with \textit{H. pylori} or those who had reduced plasma vitamin C levels.

Processed meat, an important source of N-nitroso compounds, refers to those preserved by adding nitrate, nitrite, or salt, or by smoking.\textsuperscript{102} In a meta-analysis that summarized available evidence from six prospective cohort studies and nine case-control studies published from January 1966 through March 2006, the summary relative risks for an increment in processed meat consumption of 30 g/day (approximately half of an average serving) were 1.15 (95% CI 1.04–1.27) for the cohort studies and 1.38 (95% CI 1.19–1.60) for the case-control studies.\textsuperscript{101} In the EPIC cohort, when the association between processed meat and gastric cancer was evaluated by anatomic site, each 50 g/day increase in processed meat was associated with a significant 2.45-fold increase in gastric non-cardia cancer but not with gastric cardia cancer.\textsuperscript{103}

**Body weight**

Growing evidence suggests that increasing body weight is associated with increased risk for gastric cardia cancer,\textsuperscript{5,79,105–106} but not for gastric non-cardia cancer.\textsuperscript{79,104} A systematic review of four published US and European studies that evaluated the association between body mass index (BMI) and risk of gastric cardia adenocarcinoma reported that overweight (BMI ≥25 to <30 kg/m\textsuperscript{2}) or obesity (BMI ≥30 kg/m\textsuperscript{2}) was significantly associated with a 1.5-fold increase in risk of gastric cardia adenocarcinoma.\textsuperscript{8} Three recent studies also found a positive association between BMI and risk for gastric cardia cancer.\textsuperscript{104–106} In the Netherlands Cohort Study, the relative risks of gastric cardia adenocarcinoma were 1.32 (95% CI 0.94–1.85) for overweight and 2.73 (95% CI 1.56–4.79) for obese men and women, compared to individuals with normal weight (BMI ≥20 to <25 kg/m\textsuperscript{2}).\textsuperscript{106} The parallel increase in both the incidence of gastric cardia cancer and the prevalence of obesity suggests that obesity likely contributes to some of the rising incidence of gastric cardia adenocarcinoma in the United States.\textsuperscript{107}

**CONCLUSION**

High intake of fresh fruits and vegetables, lycopene and lycopene products, and potentially vitamin C and selenium may reduce the risk for gastric cancer. By contrast, high intake of nitrosamines, processed meat products, salt and salted foods, and overweight and obesity may increase the risk. Current data provide little support for an association of \textit{β}-carotene, vitamin E, and alcohol consumption with risk for gastric cancer.

**REFERENCES**


