2 Prevention of Upper Gastrointestinal Tract Cancers

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1. INTRODUCTION

This chapter will focus on lifestyle factors associated with cancers of the esophagus and stomach. Unlike such major cancers as prostate and breast, whose etiologies remain obscure at the present time, hindering primary prevention, cancers of the upper gastrointestinal tract offer well-defined intervention opportunities. Epidemiologic studies have clearly established the important role of alcohol, tobacco, and diet, and recent findings have documented the relation between infection with *Helicobacter pylori* and cancer of the stomach. These factors and their interactions will be discussed for cancers of each of these two sites, which together account for approx 35,000 new cases and 26,000 deaths annually in the United States *(1)*.

2. CANCER OF THE ESOPHAGUS

For many years, cancer of the esophagus in the United States, and in most areas throughout the world, was virtually synonymous with squamous cell carcinoma *(2)*. Hence, most of the established risk factors for esophageal cancer are specific to this cell type, which comprised the vast majority of cases in studies of this cancer. Recent shifts in the histopathologic cell type have given rise to a rapid increase in the incidence of adenocarcinoma of the esophagus in the United States, particularly among white males *(3)*. Because of the increasing importance of esophageal adenocarcinoma, a separate section will consider this entity, which may differ in etiology from squamous cell carcinoma.

2.1. Squamous Cell Carcinoma

2.1.1. Tobacco and Alcohol Consumption

Both tobacco and heavy alcohol consumption are well-established risk factors for esophageal carcinoma. In the United States and other Western countries, over 90% of the risk can be attributed to the individual and joint effects of tobacco and alcohol *(4)*.

An early study by Wynder and Bross *(5)* graphically examined the interaction between alcohol and tobacco and the data suggest a multiplicative effect. Tuyns et al. *(6)* evaluated this relation more formally in data from a case control study in Brittany. At

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the highest level of consumption of both alcohol (≥ 121 g ethanol /d) and tobacco (≥ 30 g/d) the risk of esophageal cancer was 156 relative to non- or light consumers. The increased risk associated with alcohol consumption appears exponential whereas increased tobacco smoking appears to yield a more linear increase. Saracci *(7)* estimates that the excess risk because of the interaction of alcohol and tobacco is about 25-fold.

Data from a recent case-control study in Italy are presented in Table 1 *(8)*. Study subjects included 271 male cases and 1754 male controls with acute illnesses unrelated to tobacco and alcohol consumption. Even with a reference category that included moderate alcohol consumption (< 35 drinks/wk) by nonsmokers, the estimated relative risk (RR) of esophageal cancer among heavy smokers (≥ 25 cigarettes/d, ≥ 40 yr) and very heavy drinkers (≥ 60 drinks/wk) is 22. This report was updated in 1994 to include women *(9)*. Among alcohol drinkers (any vs none), similar risks were observed for women and men, 3.0 and 4.7, respectively; however, male abstainers had a twofold increased risk while female nondrinkers had a reduced risk, 0.7, compared with light to moderate drinkers. This study of esophageal cancer fails to support the hypothesis posed by Blume *(10)* that women may be more susceptible to the effects of alcohol, at least for this particular cancer site.

Whether the increased risk of esophageal cancer attributed to alcohol use is a function of the dose of ethanol or whether the type of alcoholic beverage and its other constituents play a role has also been examined, most recently in a Japanese study by Hanaoka et al. *(11)*. Their findings confirm those of others that indicate the amount of alcohol consumed, rather than any particular type, is the primary determinant of risk.

2.1.2. Thermal Irritation

Thermal injury as a result of drinking very hot liquids has been suggested to increase risk of esophageal cancer by increasing susceptibility to other carcinogenic exposures *(12,13)*. This hypothesis has some support in both ecologic and analytic studies. Persons living in regions of the world with high rates of esophageal cancer, such as northern Iran and Siberia, are reported to drink excessively hot tea *(14,15)*.

Martinez *(16)* found that more cases than controls reported drinking hot, rather than warm or cold, coffee in Puerto Rico. Both Segi *(17)* and Hirayama *(18)* found an increased risk of esophageal cancer in persons consuming hot tea gruel. In Latin America, several studies have examined the role of maté drinking. DeStefani et al. found a strong association between hot maté consumption and risk of esophageal cancer in Uruguay *(19)*. An earlier case-control study in Brazil found no such association *(20)*. In 1994, Castelletto et al. examined the role of maté in an Argentinean case-control study *(21)*. They found alcohol, tobacco, and barbecued meat, but not hot maté, to be the primary risks factors.

A study of chronic esophagitis, a precursor lesion for esophageal cancer, in a high-risk region in China lends support to an etiologic role of thermal injury *(22)*. A greater than fourfold excess of mild and moderate esophagitis was found in young persons 15–26 yr of age consuming burning hot beverages (odds ratio [OR] 4.39, confidence interval [CI] 95% 1.72–11.3). This study design minimizes recall/response bias because case-control status is not known at the time of interview, and suggests that this factor may be important at a relatively early stage in the development of this cancer.

2.1.3. Nutrition

2.1.3.1. Dietary Studies. Fruits and fresh vegetables are consistently associated in studies throughout the world with decreased of esophageal cancer, even after control-

Table 1
Adjusted Odds Ratios[a] for Cancer of the Esophagus by Alcohol and Tobacco Consumption[b]

	Alcohol (drinks per week)		
Smoking status	*< 35*	*35–59*	*≥ 60*
Nonsmoker	1.0[c]	2.2	2.6
Light	2.1	4.4	5.5
Moderate	4.4	9.7	11.4
Heavy	8.4	18.5	21.8

[a] Adjusted for age, residence, education, and profession.
[b] Adapted from Barón et al. *(8).*
[c] Reference category.

ling for tobacco and alcohol use. Deficiencies of vitamin C, one of several micronutrients contained in fruits and vegetables, have been reported in several areas of the world with exceptionally high rates of esophageal cancer. These include northern Iran *(14),* Linxian County, China *(23),* and northern and eastern Siberia *(15),* among others. Other dietary deficiencies are also strongly associated with esophageal cancer risk; these include iron, riboflavin, niacin, molybdenium, zinc, and other trace elements *(24).*

The 1961 report by Wynder and Bross noted significantly lower consumption levels of green and yellow vegetables among male cases compared to controls, and a nonsignificantly lower consumption level of fruit *(5).* Potatoes (RR = 0.4, $p < 0.05$) and bananas (RR = 0.3, $p < 0.01$) were determined to be protective in a case-control study in Singapore *(25).* Frequent consumption of 16 different fruits and vegetables was associated with decreased risk of esophageal cancer in Iran *(26).* Relative risks for high vs low consumption levels ranged from 0.4–0.9 and findings for 10 of the 16 foods were significantly protective.

A significant inverse trend ($p < 0.001$) was reported between monthly vitamin C consumption and esophageal cancer in white males in New York state *(27).* A weaker but significant inverse association was observed for vitamin A intake ($p = 0.03$). A fivefold reduction in risk in the highest tertile of fruit and vegetable consumption (> 81 times/mo) was also found. A more recent report from New York found no association with vitamin C derived from vegetables *(28).* However, in this study only 24% of the eligible cases were included and they may not be representative of the total series of cases.

Ziegler et al. *(29)* found significant inverse associations between relative risk of esophageal cancer and five indicators of general nutritional status, including total fruit and vegetable consumption (RR = 0.5, p-trend < 0.05). This case-control study focused on high-risk black males in Washington, DC. An index of vitamin C intake yielded an estimated relative risk of 0.55 (p-trend < 0.05) for the highest tertile of consumption. The only other micronutrient significantly inversely associated with risk was riboflavin.

Two case-control studies conducted in the high-risk region of Calvados, France, found a protective effect of vitamin C on esophageal cancer risk *(30,31).* Approximately threefold significant reductions in risk were observed at the highest level of intake of

citrus fruits and of dietary vitamin C. Similarly, DeCarli et al. *(32)* reported a relative risk of 0.3 (0.1–0.6) for high-level fruit consumption and nonsignificant reductions in risk for high-level vegetable intake. In India, Notani and Jayant *(33)* found a more modest reduction from high-level fruit intake (RR = 0.8, 0.5–1.3), but a significant risk reduction among daily consumers of vegetables (RR = 0.4, 0.2–0.7).

Two 1988 reports support the findings of others indicative of protection from high intake of dietary vitamin C and fresh fruits *(34,35).* Brown et al. *(34)* found a significant halving in risk in the highest tertile of consumption of citrus, fruit, all fruits combined, and dietary vitamin C ($p < 0.05$). A relative risk of 0.4 (0.2–0.8) for high-level consumption of raw vegetables and fresh fruit was found in the California study of Yu et al. *(35).* Li et al. *(36)* found no reduction in esophageal cancer risk associated with fruit consumption in a high-risk region of China, but a homogeneously low level of intake of fruit in this population makes it a poor one in which to evaluate the association *(37).* Strong protective effects (p-trend < 0.001) associated with consumption of citrus fruits and other fruits were reported by Cheng et al. *(38)* who conducted a large case-control study in Hong Kong. The proportion of esophageal cancer cases attributable to low-consumption levels of citrus fruits in this population was estimated to be 26%. A retrospective cohort study of esophageal cancer in Linxian, China, reported a significant reduction in risk associated with regular consumption of fresh vegetables, RR = 0.66 (0.44–0.99) *(39).*

A large Italian study of esophageal cancer in lifelong nonsmokers afforded the opportunity to evaluate other risk factors in the absence of residual confounding by tobacco use *(40).* Although the major risk factor was not unexpectedly alcohol, green vegetables and fresh fruit were associated with significantly reduced relative risks of 0.6 and 0.3, respectively. Similar reductions in risk were associated with β-carotene intake. The estimated relative risk for the combination of high alcohol and low β-carotene was 8.6, with an attributable risk of approx 45%.

Several dietary factors in addition to fruits and vegetables and their constituent micronutrients have been proposed as candidate protective factors, although the epidemiologic evidence to date is considerably more limited. One such factor is green tea, *Camellia sinensis.* Experimental studies have demonstrated antimutagenic and anticarcinogenic effects, especially in the esophagus *(41–44).* Findings in a recent population based case control study in China provide some support to this hypothesis *(45).* After adjustment for confounders including tobacco and alcohol, a significant halving of risk was observed in women drinking green tea (OR = 0.50, CI 95%: 0.30–0.83) and an inverse a dose response was observed. The findings in men were not statistically significant; however, a significant protective effect was observed in both men and women who did not smoke or drink alcohol. Since green tea, as well as other drinks, can be consumed at hot temperatures and since excessively hot fluids have been associated with increased risk of this cancer, the relation between drinking burning-hot fluids was also evaluated. The protective effect of green tea was limited to tea taken at normal temperatures.

Ginseng, which may be taken as a tea, powder, or as a slice of the root, has also been proposed as a potential anticarcinogen. Unlike the polyphenols in green tea, no specific component or mechanism has been elaborated *(46,47).* Yun and Choi *(48)* reported a case-control study in Korea where ginseng is commonly used. The relative risk of esophageal cancer associated with ginseng intake was 0.20 (CI 95%: 0.09–0.38) after adjustment for tobacco, alcohol, and other confounders. This large reduction in risk was observed in both smokers and nonsmokers. Additional studies are obviously necessary

to confirm this preliminary finding.

2.1.3.2. Biochemical Studies. A number of studies have examined biochemical nutritional indicators in blood or tissue, with particular focus on antioxidants. Chen et al. *(49)* collected blood specimens from a sample of the population in 65 different countries in China and correlated the concentration of over 10 different antioxidants with county-specific mortality rates for several cancers, including esophageal. A highly significant inverse relation was found between esophageal cancer rates and both plasma ascorbic acid and selenium in men and selenium in women. Another study in a high-risk region of China found low levels of zinc *(50).* A recent population-based case-control study conducted in Washington state *(51)* found no significant difference in nail zinc concentrations in esophageal cancer cases and controls, but a large and significant reduction in risk associated with dietary intake of zinc from foods and supplements: OR of 0.5 and 0.1 for the middle and upper tertile of consumption, respectively, trend $p < 0.001$. Other elements in nail tissue associated with esophageal cancer were iron (OR = 2.9 high vs low levels), calcium (OR = 2.6) and cobalt (OR = 1.9). Although this study suggests a number of differences in mineral levels of cases and controls reflecting differences in intake, metabolism or both, additional investigation is warranted to determine which, if any, of these findings is etiologically meaningful.

2.1.3.3. Chemoprevention Studies. Chemoprevention as defined by Sporn and Newton *(52)* is prevention of cancer with pharmacological agents used to inhibit or reverse the process of carcinogenesis. In this relatively new field, which has grown in acceptance in the 1980s and 1990s, esophageal cancer is one of the few cancer sites for which results from completed trials are available.

Muñoz et al. *(53)* reported findings from the first short-term intervention trial in 1985. A total of 610 subjects ages 35–64 in the high-risk region of Huixian, China, were randomized to receive 15 mg (50,000 IU) retinol, 200 mg riboflavin, and 50 mg zinc or placebo once per week for 13.5 mo. Five hundred sixty-seven participants completed the trial and underwent endoscopy for histological diagnosis of premalignant lesions of the esophagus (esophagitis, atrophy, dysplasia). The combined treatment had no effect on the prevalence of precancerous lesions of the esophagus. It should be noted, however, that the dose was relatively small and the intervention period short. Micronuclei in exfoliated cells of buccal and esophageal mucosa were evaluated in 170 study subjects from this same trial as an indicator of chromosomal damage *(54).* No reduction in micronuclei was found in subjects after treatment, but a significant reduction in the percentage of micronucleated cells was observed in treated subjects (0.19%) compared to the placebo group (0.31%), $p = 0.04$. In a third report from this same trial, Wahrendorf et al. *(55)* reanalyzed data by blood levels of retinol, riboflavin, and zinc at the beginning and end of the trial because improvement in blood retinol and zinc levels had been observed in the placebo group as well as the actively treated group. Individuals who had large increases in retinol, riboflavin, and zinc blood levels were more likely to have a histologically normal esophagus at the end of the trial regardless of treatment group.

Two large intervention studies conducted in the high-risk population of Linxian, China, were recently reported *(56,57).* A 6-yr randomized trial of daily vitamin/mineral supplementation vs placebo found no significant reductions in cancer incidence or mortality among adults with preexisting precancerous lesions of the esophagus *(56).* The larger trial in this same area included 29,584 subjects from the general population randomly allocated to combinations of retinol and zinc, riboflavin and niacin, vitamin C

and molybdenum, and/or β-carotene, vitamin E and selenium in doses of one to two times US Recommended Daily Allowances. Significantly reduced total mortality (RR = 0.91, 0.84–0.99) and stomach cancer mortality (RR = 0.79, 0.64–0.99) were observed in those taking β-carotene, vitamin E, and selenium. No significant effects on mortality or cancer incidence, including esophageal cancer, were observed for any of the other vitamin/mineral combinations.

Wang et al. *(58)* evaluated whether any of the vitamin/mineral supplement combinations affected the prevalence of clinically silent precancerous lesions and early invasive cancers of the esophagus and stomach as determined by endoscopy and biopsy in this same trial. No significant reductions in risk of dysplasia or cancer were observed for any of the supplements, although retinol and zinc were suggestively associated with a lower risk of gastric cancer, OR = 0.38, $p = 0.09$. Similarly, Dawsey et al. *(59)* evaluated the effect of the single vitamin/mineral supplement used in the trial of persons with esophageal dysplasia to see if treatment reduced the prevalence of histological dysplasia or early cancer of the esophagus or gastric cardia. Modest, nonsignificant risk reductions were observed compared to placebo, (OR = 0.86, 0.54–1.38). The authors conclude that longer interventions with larger number of subjects are required to adequately evaluate the effectiveness of micronutrient supplementation in this high-risk population. In subjects from this same trial, Rao et al. *(60)* evaluated whether epithelial proliferation, an early step in carcinogenesis was reduced by treatment after 30 mo of intervention. The results were similarly inconclusive.

2.2. Adenocarcinoma

2.2.1. Barrett's Esophagus and Medications

Barrett's esophagus is characterized by the replacement of the lower esophagus, which is normally stratified squamous epithelium, by metaplastic columnar epithelium *(61)*. This condition, attributed to chronic esophageal reflux, is believed to be premalignant lesion for esophageal adenocarcinoma *(62)*.

Barrett's esophagus displays a similar age, race, and gender distribution as does esophageal adenocarcinoma: it is most common in white males over age 40 *(3,63)*. The reported incidence of esophageal adenocarcinoma in patients with Barrett's is from 30 to over 100 times greater than the rate observed in the general population *(63–66)*.

There also appears to be a familial form of this disease, inherited as an autosomal dominant trait *(67–69)*. Two recent reports of families with the inherited form of Barrett's provide additional support for Barrett's as a precursor lesion *(67,69)*.

A related hypothesis has proposed that the use of medications that relax the esophageal sphincter, and thereby promote reflux, may increase risk of adenocarcinomas of the esophagus and gastric cardia *(70)*. Histamine H_2 receptor antagonists used routinely for treatment of peptic ulcer and gastroesophageal reflux disease have also been proposed as an etiologic factor *(71)*. In a 1995 report, Chow et al. *(72)* examined the relation between reflux disease and its treatment to risk of adenocarcinomas of the esophagus and gastric cardia. Significant increased risks of adenocarcinoma were associated with esophageal reflux (OR = 2.1, 1.2–3.6); hiatal hernia (OR = 3.8, 1.9–7.6); and esophagitis/esophageal ulcer (5.0, 1.5–16.4). Although a fourfold increased risk was associated with four or more prescriptions for H_2 antagonists, the odds ratio was reduced to 1.5 (0.4–5.4), after adjusting for predisposing conditions. The relation with use of anticholinergics adjusted for number of conditions was actually inverse: risk de-

creased with increasing number of prescriptions (p-trend = 0.08). The study findings support the elevated risk of adenocarcinoma conferred by reflux disease, but indicate that the mechanism is not strongly related to treatment of reflux. An interesting, but as yet unconfirmed, new finding indicates an increased risk of esophageal adenocarcinoma among long-term users of theophylline-containing drugs *(73).* The significance of this finding is linked to the rising incidence of asthma and increasing use of asthma medications in the general population and its association with reflux disease.

2.2.2. Tobacco and Alcohol

Two population-based studies of cancers of the esophagus and gastric cardia conducted in western Washington state 1983–1990 were analyzed to evaluate risk factors for adenocarcinoma compared to squamous cell *(74).* Use of alcohol and cigarettes were significantly associated with increased risk of both histologic types, but the odds ratios were markedly higher for squamous cell carcinoma. For current smokers of 80+ pack-yr compared to nonsmokers, the odds ratios were 16.9 (4.1–6.91) for squamous cell carcinoma and 3.4 (1.4–8.0) for adenocarcinoma. Similarly, for persons who reported drinking 21 or more drinks/wk compared to <7/wk, the respective odds ratios were 9.5 (4.1–22.3) and 1.8 (1.1–3.1). Population attributable risk estimates found that cigarette smoking and alcohol together accounted for 87% of the squamous cell carcinomas, while for adenocarcinoma the estimate for cigarettes was 34% and 10% for alcohol consumption of seven or more drinks/wk.

Estimates of esophageal adenocarcinoma risk for alcohol and tobacco use by Kabat et al. *(75)* were similar: current smokers, 2.3 (1.4–3.9); 4+ oz of whiskey-equivalents per week, 1.9 (1.3–4.3). Brown et al. *(76)* also report that tobacco and alcohol are likely etiologic factors, but conferring lower magnitude risk than that associated with squamous cell cancers. The odds ratios at the highest level of smoking ($\geq$ 40 cigarettes/d) and drinking ($\geq$ 29 drinks/wk) were 2.6 (p-trend $<$ 0.01) and 2.8 (p-trend $<$ 0.05), respectively. Their study included white men from Atlanta, Detroit, and New Jersey. Significantly increased risks were also found associated with history of ulcer, especially duodenal, and with low social class. The authors note that alcohol and tobacco use, although associated with esophageal adenocarcinoma, does not explain the rapid increase in these tumors.

In 1997, a multicenter study of esophageal and gastric cancers reported an increased risk of squamous cell carcinoma and adenocarcinoma of the esophagus and adenocarcinomas of all sites in the stomach among smokers *(77).* Current smokers had a two- to threefold increased risk of adenocarcinomas of the esophagus and gastric cardia compared to a fivefold increased risk of squamous cell carcinoma of the esophagus. Although risk of these squamous cell tumors declined with duration of smoking cessation, risks of esophageal and cardia adenocarcinomas remained significantly elevated for more than 30 yr after cessation. This long lag suggests that the effect of tobacco on these tumors may be on tumor initiation.

2.2.3. Obesity and Diet

Two 1995 reports have linked obesity to adenocarcinoma of the esophagus *(74,76).* A threefold increased risk ($p < 0.01$) was observed at the highest level of body mass index (> 26.6 kg/m^2) compared to the lowest in white men *(76).* No significant associations were found for dietary fat, total calories, meals eaten per day, or consumption of coffee and tea. A protective effect of high intake of raw fruit (OR = 0.4, $p < 0.05$) and

vegetables (OR = 0.4, $p < 0.05$) was observed. Vaughan et al. *(74)* report divergent associations for squamous cell and adenocarcinoma with body mass index. A significantly increased risk of adenocarcinoma was found at the highest decile of body mass index (OR = 1.9, 1.1–3.2), whereas body mass was inversely associated with squamous cell carcinoma. The population-attributable risk for body mass index above the 50th percentile was 18% for adenocarcinoma. These observations are consistent with esophageal reflux associated with obesity. These reports were confirmed in a large multicenter population-based case-control study *(78)* in which obesity measured by body mass index was found to be a strong risk factor for esophageal adenocarcinoma and a moderate risk factor for adenocarcinoma of the gastric cardia. The authors suggest that the increasing rates of adenocarcinomas of the esophagus and cardia may be explained in part by increasing prevalence of obesity in the United States population.

3. CANCER OF THE STOMACH

A steady decline in gastric cancer has been apparent in many countries for the past several decades. The declining rates were first noted in the United States as early as 1930 *(79)* and have persisted throughout this century *(1).* Survival rates have not appreciably changed *(1,80)* therefore, the decline in deaths cannot be attributed to better treatment and prolonged survival, but to actual declines in incidence that are now well documented *(81).* This decline, believed to reflect changes in environmental factors, has been referred to as an "unplanned triumph" since the shifts did not result from active medical or public health intervention and are believed to result from large shifts in food processing and consumption *(82).* It should be noted that the increase in esophageal adenocarcinoma documented in the previous section does include an increase in adenocarcinomas of the gastroesophageal junction and gastric cardia.

3.1. Histologic Types

Adenocarcinomas account for more than 97% of gastric cancers, and studies of etiology are generally limited to this histologic type *(83).* Building on an earlier observation that gastric carcinomas were often accompanied by features found in intestinal epithelium *(84),* Laurén *(85)* proposed a classification of adenocarcinomas into two subtypes, "intestinal" and "diffuse." Many, but not all tumors, can be thus classified because some tumors contain characteristics of both types and others neither. Diffuse carcinomas, sometimes referred to as "endemic," tend to occur with similar frequency throughout the world, whereas the distribution of intestinal or "epidemic" type tends to parallel the distribution of overall gastric cancer rates, i.e. this type is relatively more common in areas with high rates and lower where gastric cancer are low *(86).*

3.2. Risk Factors

3.2.1. *Helicobacter Pylori*

Spiral-shaped bacteria in contact with gastric mucosa were first reported about 100 yr ago by Pel *(87)* and ignored for the next 90 yr. In 1983, Marshall *(88)* and Warren *(89)* reported isolating these bacteria in cultures of biopsies taken from patients with gastritis and peptic ulcers undergoing endoscopy. By 1994, the International Agency for Research on Cancer, World Health Organization, had determined that infection with *H. pylori* is carcinogenic to humans, and declared it a Group 1 carcinogen based on the

large body of research developed during the 11-yr period *(90)*.

H. pylori infection is one of the most prevalent infections worldwide, with a range of 20–40% in developed countries and as high as 70–90% in some developing countries *(91,92)*. Prevalence increases with age and no difference in seroprevalence has been found between males and females *(93)*. Socioeconomic status including poor housing conditions, large family size, and low education attainment, is a predictor of prevalence of infection as well as of gastric cancer.

The role of *H. pylori* in gastric carcinogenesis has been explored in correlation and case-control studies, but this approach has yielded equivocal results, largely because of difficulties in determining temporality *(90)*. Three different cohort studies provided material for nested case-control analyses that resolved the issue of temporality. *H. pylori* infection was determined by IgG antibodies in serum collected at the time of cohort enrollment 6–14 yr earlier. Forman et al. *(96)* found an approximate threefold increased risk of subsequent gastric cancer in cohort of Welsh men; Parsonnet et al. *(97)* reported a relative risk of 3.6 (1.8–7.3) in a cohort of men and women in California; and Nomura et al. *(98)* a sixfold significantly increased risk in Japanese-American men living in Hawaii.

The mechanisms by which *H. pylori* infection increases gastric cancer risk are not well-established and are the focus of ongoing investigation. *H. pylori* infection, the main cause of chronic gastritis, has been demonstrated to decrease the concentration of ascorbic acid in gastric juice *(99–102)*. *H. pylori* infection is also associated with varying degrees of inflammation *(103)*. In inflammatory states, nitric oxide may be generated and interact with reactive oxygen species forming new cytotoxic compounds *(104,105)*. Thus, *H. pylori* infection has the potential to increase oxidative stress and decrease antioxidant capacity.

Because *H. pylori* infection is associated with several health outcomes in addition to gastric cancer, such as dyspepsia and peptic ulcers, the role of strain virulence factors has received attention. Risks of gastric adenocarcinoma and gastric atrophy, a premalignant condition, have been associated with *cagA*+ strains compared to *cagA*− ones *(106–108)*.

3.2.2. Tobacco and Alcohol

Although both tobacco and alcohol use are weakly associated with increased risk of gastric cancer, the strength and magnitude of the association is much less clear than that for esophageal cancer.

Early case-control studies of gastric cancer and alcohol intake were equivocal, with some reporting positive associations *(109,110)* and others none *(111,112)*. Continued study has yielded similar mixed results. Correa et al. *(113)* found twofold elevations in risk of gastric cancer, at the highest level of alcohol intake for both whites and blacks in Louisiana. After controlling for other risk factors, wine (OR = 2.10, 1.13–3.89) and hard liquor (OR = 1.95, 1.14–3.34) were significantly associated with risk in whites, but not in blacks. A 1990 report of stomach cancer in Los Angeles males also found an increased risk (OR = 3.0, 1.1–8.7) at the highest level of total ethanol intake and significant risks for daily consumption of beer *(114)*. The effect of alcohol was stronger for cancer of the gastric cardia than at other sites.

A twofold increased risk of stomach cancer was found for beer consumption in a German study, but wine and hard liquor were associated with decreased risk *(115)*. This is in contrast to a French study that reported a very large relative risk (1.9, 3.3–14.3) as-

sociated with heavy use of red wine *(116).*

Two cohort studies, however, suggest that alcohol is not an independent risk factor for gastric cancer. Nomura et al. *(117)* found no increased risk of gastric cancer associated with consumption of beer, wine or hard liquor in Japanese-American men living in Hawaii. Kneller et al. *(118)* likewise found no association for total alcohol or for any specific type.

More consistent findings link smoking to a 1.5 to threefold increased risk of gastric cancer *(113–118);* however, the overall increased risk has often failed to demonstrate a dose-response *(109,117,119).* The cohort study by Kneller et al. did find significant increases in risk with both increasing number of cigarettes smoked per day and pack-years of smoking *(118).* At the highest number of pack-years, the relation of risk was 2.3 (1.23–4.33) and for current use of 30 or more cigarettes/d the relative risk was 5.8 compared to nonsmokers. Although age at death did not significantly modify risk, the association with smoking was stronger for younger cases. The authors suggest that this finding may reflect a higher proportion of adenocarcinomas of the gastric cardia at younger ages and a stronger relation between smoking and cancers of the cardia than with cancers of other sites in the stomach.

3.2.3. Salted, Pickled, and Smoked Foods

Salt has been demonstrated in animal studies to enhance gastric carcinogenesis *(120–123).* It has been suggested that the action of salt as a gastric mucosal irritant facilitates the action of carcinogens and thus salt acts as a cocarcinogen *(124).*

Epidemiologic studies also suggest an increased risk of gastric cancer associated with high salt intake when salted and pickled foods are included in total intake. Death rates throughout regions of Japan *(125)* were found to be correlated with consumption of salted fish and salted vegetables. A geographic correlation has also been demonstrated in China *(126).* Consumption of salt-cured meats, salted fish, and other salt-preserved foods has been associated with increased risk in case-control studies throughout the world *(127–130).* Several studies have also reported associations with the addition of salt to foods *(127,131)* or a reported "heavy intake" *(132,133).*

Many of the strongest findings have been noted in areas of the world where there is a wide range of intake including very high levels, such as in Korea *(129).* A recent nested case-control analysis reported by Friedman and Parsonnet *(134)* failed to find evidence that routine salting led to increased risk in a California study population. "Heavy" salt intake in US populations may be quantitatively less than "heavy" intake in other areas of the world and may not be sufficient to demonstrate an increased risk. For example, salted fish and salted vegetables in Japan may contain up to 30% NaCl compared to isotonic saline which is 0.8% *(124,125).*

Numerous *N*-nitroso compounds have demonstrated carcinogenicity *(135).* Based on studies of premalignant lesions of the stomach, it has been hypothesized that intragastric synthesis of *N*-nitroso compounds is a factor in the gastric carcinogenic process *(136).*

Two recently reported studies evaluated factors associated with in vivo nitrosamine formation in humans using the test developed by Ohshima and Bartsch *(137)* that measures urinary excretion of noncarcinogenic *N*-nitrosoproline after ingesting a given dose of proline. Mirvish et al. *(138)* found that men in rural Nebraska who drank water from private wells with a high-nitrate content excreted significantly higher *N*-nitroso proline than men drinking water with a low-nitrate content. Their findings parallel those of a

study in Denmark *(139).* Sierra et al. *(140)* used the nitrosoproline test in children living in high- and low-risk areas for stomach cancer in Costa Rica. They found the concentration excreted by children in the high-risk area significantly greater ($p < 0.04$) compared to children from the low-risk area. They also found that excretion was markedly reduced when ascorbic acid, an inhibitor of nitrosation reactions was given with the proline.

Associations between gastric cancer and dietary intake of nitrate, nitrite and preformed nitroso compounds are suggestive *(141–146),* but the validity of such indexes is not well established given the multiple sources, including food, water, and endogenous formation.

3.2.4. Fruits and Vegetables

Table 2 presents an extensive compendium of dietary studies of gastric cancer *(111,117,118,129,132,141–165).* The strong, consistent inverse association between consumption of fruits and vegetables is abundantly clear. Of the 26 studies described that specifically examined foods and food groups, 24 found a decreased risk of stomach cancer associated with high intake of one or more fruits and vegetable and the vast majority were statistically significant with up to twofold reductions in risk. Only two studies reported an increased risk of gastric cancer associated with fruits *(118)* or vegetables *(128),* and their findings do little to cast doubt on the apparent protective effect of fruits and vegetables. The findings of Tajima and Tominaga *(128)* stand in contrast to many case-control studies in Japan and elsewhere, and the study by Kneller et al. *(118)* was based on a very limited dietary questionnaire that increases the likelihood of misclassification.

3.2.5. Micronutrients

Consumption of fruits and vegetables serves as a dietary source of a plethora of vitamins, minerals, fiber, and less well-studied trace compounds. Many of these are highly correlated with one another, particularly when exposure is based on dietary assessment; therefore, a finding attributed to one may actually reflect the effect of another constituent from the same foods. The strongest findings, therefore, are based on biochemical studies, e.g., blood levels prior to cancer onset and chemoprevention trials, which actually test the efficacy of specific micronutrients in prevention. The micronutrients believed to be most strongly associated with reduced gastric cancer risk based on studies to date are vitamin C, β-carotene, and vitamin E/selenium.

Findings from dietary estimates of intake are also included in Table 2. Relatively high consumption of vitamin C and β-carotene is consistently associated with reduced risk of gastric cancer *(132,141,143–145,147,150,154,155,157,160,163).* Serological assessment also supports a role. Prospective studies that have evaluated vitamin C are scant because vitamin C deteriorates quickly unless specimens are acid stabilized prior to freezing *(166).* A large well-conducted cohort study, the Basel study *(167),* did have such material available. Mean plasma vitamin C was significantly lower in persons who died of cancer than in survivors: 47.61 ± 1.78 μmol/L vs 52.76 ± 0.44 μmol/L, respectively, $p < 0.01$. The findings were also significant ($p < 0.05$) for persons who subsequently died of stomach cancer and their blood levels were even lower, 42.86 ± 4.88. Low plasma levels of vitamin C were associated with a relative risk of 2.38 for gastric cancer. Low plasma levels of carotene were similarly associated with significantly increased risk of overall mortality from cancer ($p < 0.01$) and cancer of the stomach

Table 2
Selected Epidemiological Studies of Diet and Stomach Cancer Risk

Study (reference)	*Population*	*Number of cases/controls or cohort size*	*Food or nutrient*	*Relative risk high vs low intake*
Case-Control				
Meinsma *(147)*	Holland	340/1060	Vitamin C	Inverse association
			Citrus fruit	$p = 0.1$ males
				$p = .001$ females
Higginson *(148)*	United States	93/279	Dairy foods	0.6
			Fresh fruits	Inverse association
			Raw vegetables	Inverse association
Haenszel et al. *(149)*	Japanese in Hawaii	220/440	Tomatoes	0.4 ($p < .05$)
			Celery	0.4 ($p < .05$)
			Corn	0.5 ($p < .05$)
			Onion	0.5 ($p < .05$)
			Lettuce	0.8 (NS)
			Western vegetables combined	0.4 ($p < .05$)
Graham et al. *(111)*	United States	276/2200	Lettuce	0.64 (trend $p < 0.01$)
Bjelke *(150)*	Norway and United States	162/1394	Vegetable index (Norway)	Inverse association (Norway & United States)
		259/1657	Vitamin C	Inverse association (Norway & United States)
			Fruits & vegetables (United States)	Inverse association (Norway & United States)
Haenszel et al. *(151)*	Japan	783/1566	Fruit	0.7 ($p < 0.05$)
			Plum and pineapple	0.7 ($p < 0.01$)
			Celery	0.6 ($p < 0.01$)
			Lettuce	0.7 ($p < 0.01$)
Correa et al. *(132)*	United States	391/391	Vitamin C	0.50 (trend $p < 0.05$) whites
				0.33 (trend $p < 0.001$) blacks

			Fruit index	0.47 (trend $p < 0.005$) whites
				0.33 (trend $p < 0.001$) blacks
			Vegetable index	0.50 (trend $p < 0.05$) blacks
			Smoked foods	1.98 (trend $p < 0.025$) blacks
Risch et al. *(141)*	Canada	246/246	Vitamin C	0.43 (trend $p = 0.099$)
			Citrus fruit	0.75 (trend $p = 0.006$)
			Nitrite	2.61 (1.61–4.22)
			Carbohydrates	1.53 (1.07–2.18)
Trichopoulos et al. *(142)*	Greece	110/100	Lemons	0.24 (trend $p < 0.01$)
			Oranges	0.33 (trend $p < 0.01$)
			Pasta	3.42 (trend $p < 0.001$)
			Brown bread	0.79 (trend $p < 0.01$)
			Onions	0.68 (trend $p < 0.001$)
Tajima and Tominaja *(128)*	Japan	93/186	Oranges	0.9 (NS)
			Other fruit	1.4 (NS)
			Spinach	2.5 ($p < 0.05$)
			Cabbage	2.2 ($p < 0.01$)
			Green pepper	2.0 ($p < 0.01$)
Jedrychowski et al. *(153)*	Poland	110/110	Fruit	0.3 (0.1–0.6)
			Vegetables	0.6 (0.3–1.4)
LaVecchia et al. *(154)*	Italy	206/474	Vitamin C	0.46 ($p < 0.001$)
			Fruits, index	0.53 (trend $p < 0.01$)
			Citrus fruit	0.58 (trend $p < 0.01$)
			Green vegetables index	0.33 (trend $p < 0.01$)
			Ham	1.6 ($p = 0.04$)
			Polenta	2.32 ($p = 0.007$)
			β-carotene	0.39 ($p < 0.001$)
You et al. *(155)*	China	564/1131	Vitamin C	0.5 (0.3–0.6)
			Fresh fruit	0.4 (0.3–0.6)
			Fresh vegetables	0.6 (0.4–0.8)
Buiatti et al. *(156)*	Italy	1016/1159	Raw vegetables	0.6 (trend $p < 0.001$)
			Citrus fruits	0.6 (trend $p < 0.001$)
			Other fresh fruits	0.4 (trend $p < 0.001$)

(continued)

Table 2 *(continued)*

Study (reference)	*Population*	*Number of cases/controls or cohort size*	*Food or nutrient*	*Relative risk high vs low intake*
Graham et al. *(157)*	United States	293/293	Raw vegetables	0.43 (0.23–0.78)
			Fruits	No association
			Vitamin C	No association
			Carotene	0.79 (0.63–0.98)
			Sodium	1.51 (1.20–1.91)
			Retinol	1.47 (1.17–1.85)
			Fat	1.37 (1.08–1.74)
Chyou et al. *(142)*	Japanese in Hawaii	111/361	Vegetable index	0.7 (trend $p < 0.001$)
			Fruit index	0.8 (trend $p = 0.20$)
			Nitrite	No association
Buiatti et al. *(143)*	Italy	1016/1159	Vitamin C	0.5 (trend $p < 0.001$)
			α-tocopherol	0.6 (trend $p < 0.01$)
			β-carotene	0.6 (trend $p < 0.01$)
			Protein	2.6 (trend $p < 0.001$)
			Nitrites	1.9 (trend $p < 0.001$)
Wu-Williams et al. *(158)*	United States	137/137	Fruit index	0.7 (NS)
			Beef	1.6 (1.0–2.6)
Buiatti et al. *(144)*	Italy	923/1159	Vitamin C	0.5 (0.3–0.6) intestinal type
				0.5 (0.3–0.7) diffuse type
			Citrus fruits	0.5 (0.4–0.7) intestinal type
				0.6 (0.4–0.9) diffuse type
			Other fresh fruits	0.5 (0.4–0.7) intestinal type
				0.4 (0.3–0.6) diffuse type
			Raw vegetables	0.6 (0.4–0.8) intestinal type
				0.6 (0.4–0.9) diffuse type
			α-tocopherol	0.5 (0.3–0.8) intestinal type
				0.5 (0.2–0.8) diffuse type

			β-carotene	0.7 (0.5–0.8) intestinal type 0.6 (0.4–0.7) diffuse type
			Nitrites	1.8 (1.2–2.8) intestinal type 2.8 (1.5–5.0) diffuse type
			Protein	2.4 (1.02–5.6) intestinal type 5.8 (1.8–1.84) diffuse type
Negri et al. *(159)*	Italy	564/6147	Green vegetables	0.4 (0.3–0.6) (trend $p < 0.001$)
			Fruit	0.4 (0.3–0.5) (trend $p < 0.001$)
Boeing et al. *(160)*	Germany	143/579	Vitamin C	0.37 (trend $p < 0.01$)
			Citrus fruit	0.46 (trend $p < 0.01$)
			Cheese	0.44 (trend $p < 0.01$)
			Processed meat	1.74 (trend $p < 0.01$)
			Whole wheat bread	0.37 (trend $p < 0.001$)
Gonzalez et al. *(161)*	Spain	354/354	Cooked vegetables	0.5 (trend $p = 0.02$)
			Noncitrus fresh fruits	0.6 (trend $p = 0.006$)
			Dried fruits	0.4 (0.2–0.8)
			Meat	0.6 (trend $p = 0.02$)
Hoshiyama & Sasaba *(162)*	Japan	251/483	Fruits	Inverse association
			Raw vegetables	Inverse association
			Pickled vegetables	Increased risk
LaVecchia et al. *(163)*	Italy	723/2024	β-carotene	0.38 (trend $p < 0.001$)
			Vitamin C	0.53 (trend $p < 0.001$)
			Methionine	2.40 (trend $p < 0.001$)
Lee et al. *(129)*	Korea	213/213		
Hansson et al. *(164)*	Sweden		Total vegetables	0.58 (0.37–0.89) (trend $p = 0.01$)
			Citrus fruits	0.49 (0.29–0.81) (trend $p = 0.004$)
Hansson et al. (145)	Sweden		Vitamin C	0.47 (0.30–0.76) (trend $p = 0.003$)
			β-carotene	0.73 (0.45–1.18) (trend $p = 0.10$)
			Nitrates	0.97 (0.60–1.59) (trend $p = 0.99$)
Lopez-Carrillo et al. (165)	Mexico	220/752	Chili peppers (ever, never)	5.49 (2.72–11.06)
			Chili peppers (high vs none)	17.11 (7.78–37.59)

(continued)

Table 2 *(continued)*

Study (reference)	*Population*	*Number of cases/controls or cohort size*	*Food or nutrient*	*Relative risk high vs low intake*
Gonzales et al. (146)	Spain	354/354	Nitrosomines	2.1 (trend $p = 0.007$)
			Fiber	0.35 (trend $p < 0.001$)
			Folate	0.50 (trend $p = 0.008$)
			Vitamin C	0.58 (trend $p = 0.017$)
Cohort				
Nomura et al. (117)	Japanese in Hawaii	150/7990	Fruit index	0.8 (0.5–1.3)
			Fried vegetables	0.8 (0.4–1.6)
Kneller et al. (118)	United States	75/17,633	Fruit index	1.5 (trend *p*, NS)
			Vegetable index	0.9 (trend *p*, NS)
			Carbohydrates	1.6 (trend $p < 0.05$)

($p < 0.01$), with a relative risk of 2.95. No association was observed between plasma levels of vitamin A or E and gastric cancer.

Haenszel et al. *(168)* measured serum micronutrient levels in persons with various premalignant gastric lesions. Carotene levels in both men and women and vitamin E levels in men were significantly lower in subjects with gastric dysplasia than in subjects with normal mucosa or less advanced lesions.

A recent report from Japan *(169)* evaluated prediagnostic serum selenium and zinc levels and found no excess risk of stomach cancer in those with the lowest levels of selenium (OR = 1.0) or zinc (OR = 1.2).

The most compelling evidence to date for specific micronutrients in chemoprevention of gastric cancer comes from the previously described population trial in China *(57)* that found a significant reduction in stomach cancer mortality among persons taking a combination of β-carotene, vitamin E, and selenium. No reduction in risk was observed among persons taking vitamin C; however, there was no attempt in this trial to eradicate *H. pylori* that is known to decrease the concentration of ascorbic acid in gastric juice, either by increased oxidation, impaired secretion from blood into the gastric cavity, or both *(99–102)*.

4. RECOMMENDATIONS

Primary prevention of esophageal cancer obviously begins with prevention of tobacco use by teenagers and cessation among addicted adults. Use of nicotine patches and gum in conjuction with behavioral modification may improve the success rate for smokers attempting to quit. A reduction in tobacco use by teenagers has proven a persistent challenge because education programs are offset by well-funded, effective, targeted marketing by tobacco companies. The terms of the 1998 Tobacco Settlement have the potential to reduce if not eliminate these marketing approaches. Limiting alcohol consumption to moderate levels is particularly important in smokers, and physicians should actively counsel patients accordingly. Physician prompting and participation in smoking cessation efforts have proven effective.

Intake of fresh fruits and vegetables in the United States continues to fall short of the recommended "5-A-Day" *(170)*. Increased consumption should continue to be promoted and benefits are expected to accrue in reduced rates of both of these upper digestive tract cancers as well as other epithelial tumors. Effective population-based approaches are important, and since dietary patterns are often established in childhood, promotion of healthy choices in school-based food service programs is an opportunity that should not be missed.

The current dietary recommendations of the American Cancer Society, the American Heart Association, and the National Cancer Institute are remarkably similar in direction, but differ in specificity. They are included for reference in Table 3.

The efficacy of vitamin/mineral supplements has not yet been established in clinical trials; however, in case-control and cohort studies the individuals in the highest level of intake of specific micronutrients often combine high dietary intake with supplements. With the obvious caution to avoid excessive intake, a multivitamin/mineral supplement, or specific antioxidant supplement may complement dietary intake, particularly among persons with excessive oxidative stress, such as smokers.

In the United States, the treatment and eradication of *H. pylori* is currently recom-

Table 3
Dietary Recommendations of Selected Health Agencies

Agency	*Obesity*	*Fat*	*Fruits and vegetables*	*Dietary fiber*	*Alcohol*
American Cancer Society, 1996	Be physical active: achieve and maintain a healthy weight • Be at least moderately active for 30 min or more on most days of the week • Stay within your healthy weight range	Limit your intake of high fat foods, particularly from animal sources: • Choose foods low in fat • Limit consumption of meats, especially high fat meats	Choose most of your foods from plant sources: • Eat five or more servings of fruits and vegetables each day • Eat other foods from plant sources such as breads, cereals, grain products, rice, pasta, or beans several times each day		Limit consumption of alcoholic beverages, if you drink at all
National Cancer Institute, 1987	Avoid obesity	Reduce fat intake to 30% of calories or less	Include a variety of fruits and vegetables in the daily diet	Increase fiber to 20–30 g/d with an upper limits of 35 g	Consume alcoholic beverages in moderation, if at all
American Heart Association, 1996	Total calories should be adjusted to achieve and maintain a healthy body weight	Total fat intake should be no more than 30% of total calories • Saturated and polyunsaturated fatty acid intakes should be up to 10% of total calories • Monounsaturated fatty acids make up to 15% of total calories • Cholesterol intake should be less than 3000 mg/d	None	Carbohydrate intake should make up 55–60% or more of calories, with emphasis on increasing sources of complex carbohydrate Total dietary fiber intake should be 25–30 g a day from food, not supplements	If you drink do so in moderation (no more than two drinks/d)

mended only for persons with gastric and duodenal ulcers, but not for persons with nonulcer dyspepsia *(171).* Although the spectrum of clinical outcomes associated with *H. pylori* infection is wide ranging, from asymptomatic to gastric cancer, treatment and eradication of infection when possible seems prudent because the cofactors that predispose an infected individual to gastric cancer have not yet been established. This approach is currently followed in Europe.

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