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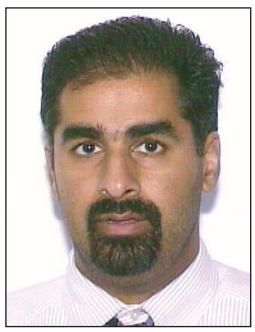
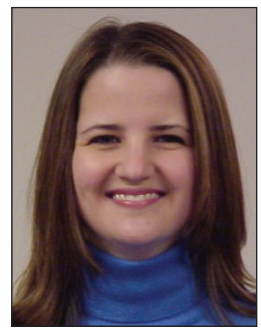
Nutrition in the Chemoprevention of Gastrointestinal Cancer: Where Are We in the New Millennium


Tarun Mullick


Emily Gasser

With the increasing awareness and detection of gastrointestinal cancer, patients and physicians are asking what role diet plays in its development. The objective of this review is to provide a summary of the research to date in regards to nutrition and the prevention of gastrointestinal cancer. The gastrointestinal cancers that are addressed in this article include: esophageal cancer (squamous and adenocarcinoma), colorectal cancer, gastric cancer (adenocarcinoma), and pancreatic cancer. Based on the review of the best available literature, certain suggestions can be made to physicians and patients regarding nutritional prevention of gastrointestinal cancer.

INTRODUCTION

Numerous studies have been done to examine what role diet plays in protection against gastrointestinal cancers. In order to make the best suggestions for physicians and patients, a careful review of the data is provided. The area of diet and cancer prevention is evolving, and, at the current time, much of the data is epidemiological or from basic science animal models. Some of the data is from humans in retrospective format, prospective cohorts, and a few randomized placebo controlled studies. In order to understand the evolution and how suggestions are being formed, it is essential to review all of the studies available as each type has value. This article provides a review of the best data available and makes suggestions based on the literature at hand in regards to nutrients, diet, and cancer prevention in the new millennium.

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This article has been dedicated to the loving memory of Swaran Lata Khokha, grandmother of Tarun Mullick who succumbed recently to pancreaticobiliary cancer.

ESOPHAGEAL CANCER

Esophageal cancer is divided into two categories: squamous cell cancer and adenocarcinoma. While squamous cell cancer had been the most common type of esophageal cancer, the incidence of esophageal adenocarcinoma has been dramatically rising over the past two decades (1).

Esophageal Squamous Cell Cancer

Tobacco and alcohol have long been known to be the greatest risk factors in the development of squamous cell cancer of the esophagus, likely accounting for the majority of the risk. In addition, the consumption of hot liquids leading to thermal injury has also been associated with increased risk (2–5).

Fruit and vegetable consumption has been demonstrated to have a protective effect in numerous case-control and cohort studies. A case control study of 844 subjects, aged 30–75, in Linzhou City (known to have one of the highest incidences of esophageal squamous cell cancer) was conducted to investigate potential risk factors in this area. Patients with esophageal cancer diagnosed between January 1998 and April 1999 were matched according to age, sex, and village of residence. In this study, the consumption of beans, vegetables and vinegar all showed a beneficial effect (odds ratios of 0.37, 0.44 and 0.37 respectively) (6).

In 1998, 111 patients in Uruguay with squamous cell carcinoma of the esophagus and 444 controls with conditions unrelated to tobacco smoking, alcohol drinking, or recent changes in the diet were matched according to age, gender, residence, and urban/rural status. Vegetables and, more markedly, fruits were associated with significant reductions in risk (7). Further support of the beneficial effects of fruits and vegetables comes from a case-control study conducted between 1992 and 1999 in the Swiss Canton of Vaud. The study consisted of 101 incident, histologically-confirmed cases (92 squamous cell, 9 adenocarcinomas) and 327 controls admitted to the hospital for acute, non-neoplastic conditions. Multivariate odds ratios (OR) were computed after allowance for age, sex, tobacco, alcohol and non-alcohol energy. The consumption of raw and cooked vegetables, citrus and other fruits lessened risk (OR = 0.5) (8). This same study found a significantly increased risk for esophageal squamous cell cancer related to the consumption of red meat (OR = 1.7 for an increase of one serving per day), pork and processed meat (OR = 1.6), and eggs (OR = 1.5) (8). The consumption of spicy foods, excessive amounts of chili, hot foods and beverages, and leftover food (number of days not defined) was positively associated with esophageal cancer risk (9).

A population-based matched case-control study of histologically confirmed squamous cell carcinoma of the esophagus in women was carried out in four regions in England and Scotland with 159 case-control pairs. Intake of salads (OR = 0.42) and a light breakfast (compared to no breakfast) (OR = 0.18) were protective (5). In a study of patients with esophageal cancer in India, green leafy vegetables and fruits were protective against esophageal cancer (9). Overall, in the literature to date, there have been at least 26 similar case-control and cohort studies that have confirmed a beneficial effect of fruits and vegetables in the prevention of esophageal squamous cell cancer (10–12).

A number of observational studies exist on particular nutrients and their potential roles in prevention of esophageal squamous cell cancer. In Linxian, China, food consumption data were collected among 104 households in spring and 106 households in autumn using a method of food inventory changes (13). Low nutrient intakes were found for selenium, zinc, riboflavin, and calcium in both spring and autumn respectively. With the onset of autumn, vitamin A, vitamin C, protein, and vitamin E consumption decreased, largely due to seasonal variations in the availability and consumption of leafy vegetables, root vegetables, and eggs. Diets in Linxian are inadequate for a number of vitamins and minerals including those shown to be associated with esophageal cancer. This study may provide some evidence as to which specific nutrients are protective.

To date there have been only a few prospective trials investigating the potential benefits of individual nutrients. In Huxian, China, the effects of riboflavin, zinc, and retinol were compared to placebo in a double-blind, randomized trial of 610 patients (14). This study found no significant difference in premalignant lesions seen on follow-up endoscopy in the esophagus, but showed a significant decrease in the percentage of micronucleated cells (15). In a nationwide population-based case-control study in Sweden, with 165 cases of

esophageal squamous cell carcinoma compared to 815 control subjects, those with a high intake of vitamin C, beta-carotene, and alpha-tocopherol showed a 40%-50% decreased risk of esophageal squamous cell carcinoma as compared to those with low intake (16).

In Linxian, China, 30,000 patients with no known disease were given either placebo versus one of four chemopreventive nutrient combinations: beta-carotene, vitamin E, and selenium; riboflavin and niacin; vitamin C and molybdenum; retinol and zinc. (17). There was no change in the incidence or mortality of esophageal cancer. Further investigation in Lixian, China examined 3,300 patients with evidence of dysplasia in the esophagus with combinations of 14 vitamins and 12 minerals in a randomized manner (18). There was no change in the incidence or mortality of esophageal cancer upon follow-up in 6 years.

Studies of individual foods and their mechanism of action in carcinogenesis at the cellular level are limited. Recently, however, lyophilized black raspberries were shown to inhibit events associated with both the initiation and promotion/progression stages of squamous cell carcinogenesis in rats (19). More studies are underway to determine if a specific nutrient in foods truly affects cancer formation.

Esophageal Adenocarcinoma

The rise in esophageal adenocarcinoma has been associated with an increased prevalence of gastroesophageal reflux disease (GERD). Barrett's esophagus is a premalignant change found in patients with chronic GERD that has been associated with an increased risk of esophageal adenocarcinoma. It is characterized by the change from squamous epithelium to specialized intestinal metaplasia.

Because of the association of GERD and esophageal adenocarcinoma, studies have been done to examine whether particular foods known to cause temporary symptoms of reflux are associated with adenocarcinoma. Consumption of foods known to relax the lower esophageal sphincter (LES) and other dietary habits potentially associated with reflux were examined in a nationwide, population-based, case-control study in Sweden. In this trial, 815 controls were compared to 185 and 258 patients with esophageal adenocarcinoma and gastric cardia adenocarcinoma, respectively. Dietary factors associated with LES relaxation and transient gastroesophageal reflux were not associated with any statistically significant risk of esophageal malignancy (16). On the other hand, another recent study from Sweden found cereal fiber to be associated with a moderately decreased risk of esophageal adenocarcinoma, as well as a significantly decreased risk of gastric cardia adenocarcinoma (20).

A few studies are available relating obesity and esophageal adenocarcinoma (21–22). More specifically, intake of excessive calories and dietary fat is associated with a significant increase in esophageal adenocarcinoma, after accounting for several potential confounding factors (23).

A case-control study in eastern Nebraska studied the relationship between diet and adenocarcinoma of the esophagus and distal stomach among 124 esophageal adenocarcinoma cases, 124 distal stomach cancer cases, and 449 controls. Statistically significant inverse associations with risk of esophageal adenocarcinoma were found for dietary intakes of total vitamin A, beta-cryptoxanthin, riboflavin, folate, zinc, dietary fiber, protein, and carbohydrate (24). Furthermore, data from a nationwide population-based case-control study in Sweden, with 185 cases of esophageal adenocarcinoma compared to 815 control subjects, showed that a high parallel intake of vitamin C, beta-carotene, and alpha-tocopherol resulted in a 40%–50% decreased risk of esophageal adenocarcinoma, compared to a low parallel intake (25). In a pilot feasibility study, 10 patients given 25 mg per day of beta-carotene for six months with known Barrett's esophagus had at least a partial regression of Barrett's epithelial islands. Molecular studies revealed the upregulation of heat shock protein 70, a chaperone protein known to stabilize the quarternary structure of proteins (26).

Zinc deficiency has been examined specifically in a mouse model and found to be associated with increased cellular proliferation in the distal esophagus and the gastric cardia, suggesting an association with adenocarcinomas in those areas (27). Zinc deficiency has been specifically associated with cyclin D1 overexpression and p53 deficiency, which increases cell proliferation (27,28). Furthermore, zinc deficiency has been found to dysregulate the p16ink4a-cyclin

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D1/Cdk4-Rb pathway, thereby promoting esophageal tumors (29). Zinc replenishment in zinc deficient rats rapidly induces apoptosis in esophageal epithelial cells and substantially reduces the development of esophageal cancer (30).

Vitamin E supplementation has similarly inhibited carcinogenesis, especially in a moderately selenium-supplemented group. Vitamin E may exert its effect through its antioxidative properties (31).

COLORECTAL CANCER

Colorectal cancer, the second leading cause of cancer deaths in the United States, is now curable when caught early. The widespread availability of colonoscopy has aided in the detection and early treatment of colorectal cancer (32). Therefore, a number of cohort and case-control studies and some larger randomized placebo-controlled studies have been performed to determine which nutritional factors are associated with a decreased risk of colorectal cancer.

Data from both retrospective and prospective studies have consistently shown that excessive adiposity (visceral adiposity especially) and physical inactivity increase the risk of colorectal cancer (33-39). A higher body mass index (BMI) has been related to an increased risk of colorectal cancer. The increased risk generally has been small but significant, with the highest quintile of BMI having a two-fold increase in risk over the lowest quintile. Interestingly, the visceral distribution of adiposity appears to be a risk factor independent of BMI. One study found that men in the highest quintile of waist/hip ratio had a three and a half time higher relative risk of colorectal cancer than men in the lowest quintile (35).

In the analysis of obesity, two key factors have been studied: energy intake and energy utilization. In a review article, Potter found a direct relationship between colorectal cancer incidence and the consumption of dietary fat and red meat in half of the studies examined (40). In larger prospective cohort studies, red meat consumption was again found to have a direct relationship with the development of colorectal cancer (40).

Other trials have shown weaker associations between saturated fat consumption and colorectal cancer incidence. For example, in the Nurses Health Study (89,000 women), red meat consumption had a relative risk of 2.49 (comparing the highest quintile to the lowest quintile) and animal fat had a relative risk of 1.89; but in the multivariate analysis, these increases in risk were not statistically significant (41). Similar data emerged from the Health Professionals Follow-up Study (42). Red meat consumption may promote carcinogenesis by forming heterocyclic amines or N-nitroso compounds (43, 44).

In 1998, the COMA report concluded that while there was no consistent relation seen in regards to energy utilization studies, there was a large consistent body of evidence that physical exercise (recreational or occupational) was protective against colorectal cancer (45). This was further corroborated in a separate review that examined this issue and found over 50 studies supporting that the more physical activity one participated in, the better the protection (46). Martinez and colleagues determined that brisk walking or jogging for 3–4 hours per week may be all that is necessary to significantly reduce risk (38).

Recently, there have been animal studies that suggest a beneficial effect of omega-3 fatty acids and monounsaturated fat in regards to colon cancer formation (47). One eloquent study done in a rat model demonstrated that saturated fat and omega-6 polyunsaturated linoleic acid (found in corn oil and safflower oil) correlated with the initiation and promotion phases of colorectal carcinogenesis (47). On the other hand, omega-3 fatty acids and monounsaturated fat correlated with inhibition of colon carcinogenesis in the rat model.

Caygill, et al demonstrated that omega-3 fatty acids and fish consumption were associated with a decreased risk of colon cancer in humans (48). A prospective study on nurses in the United States also corroborated the beneficial effects of omega-3 fatty acids and fish (41). This beneficial effect may be through the production of prostaglandin PGE3, which decreases crypt cell proliferation rate and through the inhibition of prostaglandin PGE2, which is associated with colon cancer and polyp formation (49,50,51).

A number of case-control and cohort studies have demonstrated an inverse relationship between the consumption of vegetables and colorectal cancer. The COMA report summarized the data from 28 studies and found that

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23 out of 28 studies supported this relationship (45). Trock and colleagues performed a meta-analysis of case-control studies and found an odds ratio of 0.48 for the highest quintile versus the lowest (52). More specifically, lutein-containing vegetables (spinach, broccoli, lettuce, tomatoes, oranges and orange juice, carrots, celery, and greens) have been found to yield the greatest risk reduction (OR = 0.83). This study examined the US Department of Agriculture-Nutrition Coordinating Center Carotenoid Database (1998 updated version) comparing 1,993 subjects with primary incident colon cancer versus 2,410 healthy subjects (53). The Carotenoid Database can be accessed at http://www.nal.usda.gov/fnic/foodcomp/Data/car98/car98.html .

A review by Hill that examined 58 studies on diet found that cereal fiber exerted a protective effect in 16 of 19 studies that looked at this variable (54). However, larger prospective observational studies such as the Nurses Health Study and the Iowa Women's Study have found little association with fiber from fruit, vegetable, or cereal (41,55). Overall, the European Cancer Prevention Consensus Conference concluded that cereal fiber is associated with a reduced risk of colon cancer (56). They suggest that the mechanism of protection is related to fiber's ability to bulk the stool and thereby dilute carcinogens exposed to the colon.

Calcium and vitamin D supplementation may be of benefit in colon cancer prevention. In 913 patients with known colon polyps, supplementation of 1200 mg elemental calcium resulted in adenoma recurrence of 31%. This was statistically significant in comparison to the placebo-supplemented control group, which had a recurrence rate of 38% (57). The European Calcium Fiber Polyp Prevention Trial supported this data (58). Calcium may exert its beneficial effects by activating a calcium receptor in the colon, which can inhibit the growth of transformed colon cells (59). Vitamin D may also exert a beneficial effect by inhibiting the cell cycle in transformed cells and by promoting apotosis (59).

Folate has been associated with the prevention of colorectal cancer. The best data comes from the Pooling Project of Prospective Studies, which collated the data from nine cohort studies from Europe and North America (60). After following 503,237 men and women for 13 years, those subjects in the highest quintile of intake had a relative risk of 0.79 (p= 0.002). The beneficial effect of supplemental folic acid likely occurs by providing methyl donation to DNA synthesis and repair, promoting the normal DNA-methylation process and preventing chromosome and chromatin changes (59).

GASTRIC CANCER

Gastric adenocarcinoma remains the second leading cause of cancer worldwide. Its prevalence has decreased precipitously since the 1930s in the United States with the exception of proximal cardia tumors, which have correlated with the rise in esophageal adenocarcinoma (1). In this section, we will focus specifically on the non-cardia gastric adenocarcinomas.

Foods that are smoked, dried, or pickled, and therefore containing a large amount of preserved salt, have been associated with an increased risk of gastric cancer (61–63). The nitrates and nitrites found in preserved foods have also been associated with an increased risk of gastric cancer (64).

Reduced levels of ascorbic acid (Vitamin C) have been associated with development of the distal intestinal type of gastric cancer. The majority of the 12 case-control studies reviewed recently on the protective benefit of high vitamin C consumption demonstrate a benefit, with a risk reduction of approximately 50% (65,66). Ascorbic acid secretion occurs normally in the stomach, but with *H. pylori* gastritis, its secretion is impaired (67,68). *H. pylori* has been implicated in gastric cancer development, and restoration of normal ascorbic acid levels in the stomach has been postulated to combat the effects of *H. pylori* and other gastric or ingested mutagens.

Vegetable and fruit intake has consistently been associated with a decreased incidence of gastric cancer. Over 45 case-control and prospective studies have demonstrated this benefit (69). In an Italian study of over 1,000 patients with gastric cancer and a similar number of control patients, the relative risk reduction ranged between 0.4 to 0.6 for highest intake of fruits and 0.6 to 0.8 for highest intake of vegetables (61,70).

There may also be benefit from beta-carotene, vitamin E, and selenium. In Linxian, China, 30,000 peo-

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Table 1
Summary of nutrition and prevention of gastrointestinal cancer in 2004

- Fruit and vegetable consumption is strongly associated with a reduction in the development of esophageal, stomach, and colon cancer and may be beneficial for pancreatic cancer. Most studies advise 4–5 servings of fruits and vegetables per day.
- Diets high in saturated fat and red meat are associated with an increased risk of esophageal, colon and pancreatic cancer.
- Specific to esophageal squamous cell cancer
  - Vitamin C, beta-carotene, alpha-tocopherol, zinc, and riboflavin may be chemopreventive. Lyophilized black raspberries may also be chemopreventive.
- Specific to esophageal adenocarcinoma
  - Dietary factors causing transient reflux are not associated with an increased risk of cancer, but given that chronic GERD is associated with adenocarcinoma, measures to minimize dietary triggers of GERD particular to a patient are advisable.
  - Obesity and excessive caloric intake have been associated with esophageal adenocarcinoma.
  - Vitamin C, beta-carotene, zinc, alpha-tocopherol, and cereal fiber may be chemopreventive.
- Specific to colorectal cancer
  - Obesity and physical inactivity have been related to an increased risk of colorectal cancer.
  - Omega-3 fatty acids, monosaturated fat, and fish consumption (containing omega-3 fatty acids) may decrease the incidence of colon cancer.
  - Cereal fiber may lessen colon cancer formation.
  - Calcium and vitamin D supplementation and folic acid may be chemopreventive.
- Specific to gastric cancer
  - Consumption of smoked, pickled, dried, and preserved foods increases risk of gastric cancer.
  - Vitamin C, selenium, vitamin E, beta-carotene, and cereal fiber may be chemopreventive.
- Specific to pancreatic cancer
  - Vitamin C, selenium, vitamin E, and beta-carotene may be chemopreventive.

ple followed for 5 years with supplementation had a 16% decrease in incidence of gastric cancer (17). Further exploration in this area is needed.

PANCREATIC CANCER

Pancreatic cancer is one of the most devastating cancers, with a dismal 5-year survival of only 5% (71). However, very few prevention studies are available.

Higher meat intake was associated with an increased risk of pancreatic cancer in one study that examined dietary history in 23 different countries (72). Grilled and barbequed meats may also increase risk (73).

On the other hand, high dietary fiber intake likely decreases the risk of pancreatic cancer (74). Additionally, higher levels of vegetable and fruit intake likely reduces pancreatic cancer risk as suggested in two reviews of case-control studies (75,76).

There have been some studies that indicate vitamin E, selenium, beta-carotene, vitamin C, and folate may confer a protective effect against pancreatic cancer (75,77–79). However, more data is necessary to draw any conclusions on these specific nutrients. Conflicting data have been put forth on the subject of coffee consumption (75,80,81).

PRACTICAL CONSIDERATIONS

The majority of evidence on the topic of nutrition and the prevention of gastrointestinal cancers has been gathered on populations quite different from modern Western culture. While the deficient diets of these groups do provide an ideal setting for study, it should be recognized that other environmental factors could certainly play a role in gastrointestinal cancer development. On the other hand, those studies that have examined the relationship of obesity and gastrointestinal cancer risk may have utility in application to Western culture. Further studies are needed to determine whether supplemental intake of specific vitamins and minerals will provide protection against these cancers.

In addition, recent trends in diet and food consumption deserve to be reexamined given the mounting evidence that fruits, vegetables, and whole grains protect against gastrointestinal cancers. High protein/low carbohydrate diets are known for signifi-

Table 2
Associations between select variables and risk of gastrointestinal cancers*

	Esophageal Squamous Cancer	*Esophageal Adenocarcinoma*	*Colorectal Cancer*	*Gastric Cancer*	*Pancreatic Cancer*
Fruits and Vegetables	↓	↓	↓	↓	↓
Saturated Fat	↑	↑	↑	——	↑
Red Meat	↑	↑	↑	——	↑
Obesity	——	↑	↑	——	——
Processed Foods	——	——	——	↑	——
Cereal Fiber	——	——	↓	——	↓
Vitamin C	↓	↓	——	↓	↓
Beta-carotene	↓	↓	——	↓	↓
Zinc	↓	↓	——	——	——
Alpha-tocopherol	↓	↓	——	——	——
Riboflavin	↓	——	——	——	——
Raspberries	↓	——	——	——	——
Vitamin E	——	——	——	↓	↓
Selenium	——	——	——	↓	↓
Vitamin D	——	——	↓	——	——
Calcium	——	——	↓	——	——
Folic Acid	——	——	↓	——	——

*↑ = increased risk; ↓ = decreased risk; —— = no association

cantly limiting intake of fruits, whole grains, and certain vegetables. While these diets are often used to induce rapid weight loss, the evidence in this review calls to question the long-term safety of such restrictive eating habits but also whether weight loss, in itself, could provide protection against gastrointestinal cancer.

CONCLUSIONS

While there are a number of studies examining the role of nutrition in the prevention of gastrointestinal cancer, there are, as of yet, only suggestions for dietary alterations as most of the data provide only associations. Further studies are underway to provide more concrete recommendations. Tables 1 and 2 summarize the key conclusions based on the best data available in 2004. The relationships between nutrition and gastrointestinal cancers are stated only as associations in the tables provided. ■

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