Nutrient Intake and Risk of Subtypes of Esophageal and Gastric Cancer[1]

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Abstract

Incidence rates for adenocarcinoma of the esophagus and gastric cardia have been rising rapidly. We examined nutrient intake as a risk factor for esophageal and gastric cancers in a population-based case-control study in Connecticut, New Jersey, and western Washington state. Interviews were completed for cases with histologically confirmed esophageal adenocarcinoma ($n = 282$), adenocarcinoma of the gastric cardia ($n = 255$), esophageal squamous cell carcinoma ($n = 206$), and noncardia gastric adenocarcinoma ($n = 352$), along with population controls ($n = 687$). Associations between nutrient intake and risk of cancer were estimated by adjusted odds ratios (ORs), comparing the 75th *versus* the 25th percentile of intake. The following nutrients were significantly inversely associated with risk of all four tumor types: fiber, β-carotene, folate, and vitamins C and B6. In contrast, dietary cholesterol, animal protein, and vitamin B12 were significantly positively associated with risk of all four tumor types. Dietary fat [OR, 2.18; 95% confidence interval (CI), 1.27–3.76] was significantly associated with risk of esophageal adenocarcinoma only. Dietary nitrite (OR, 1.65; 95% CI, 1.26–2.16) was associated with noncardia gastric cancer only. Vitamin C supplement use was associated with a significantly lower risk for noncardia gastric cancer (OR, 0.60; 95% CI, 0.41–0.88). Higher intake of nutrients found primarily in plant-based foods was associated with a reduced risk of adenocarcinomas of the esophagus and gastric cardia, whereas higher intake of nutrients found primarily in foods of animal origin was associated with an increased risk.

Introduction

Incidence rates for esophageal adenocarcinoma have risen steeply (>350%) since the mid-1970s (1). Rates for gastric cardia adenocarcinoma have also increased, although less rapidly. Over the same time period, incidence rates for squamous cell carcinoma of the esophagus and noncardia gastric adenocarcinomas have remained stable or declined (1).

Given the dramatic trends in incidence, we and others initiated large studies in the 1990s to identify risk factors for adenocarcinomas of the esophagus and gastric cardia. Results are now beginning to emerge from several studies and indicate that obesity (2–6) and GERD[3] (7–9) are important risk factors for these cancers. Cigarette smoking is also a causal factor, although the risk is less pronounced than for squamous cell carcinoma of the esophagus (6, 10). Use of aspirin and other nonsteroidal anti-inflammatory drugs is inversely associated with risk of adenocarcinomas of the esophagus and gastric cardia (11) as is infection with *cagA*$^+$ strains of *Helicobacter pylori* (12).

Dietary factors are considered important in the etiology of esophageal and gastric cancers. Only a few studies, however, have specifically examined the relationship between diet/nutrients and adenocarcinomas of the esophagus and gastric cardia. One recent study from Sweden evaluated the association between intake of antioxidant nutrients (vitamins C and E and β-carotene) and esophageal and gastric cancers and reported that these nutrients were inversely associated with the risk of both adenocarcinoma and squamous cell carcinoma of the esophagus but not of gastric cardia adenocarcinoma (13). Another Swedish case-control study of antioxidant nutrient intake and the risk of gastric cancer reported that vitamin C was inversely associated with the risk of gastric cardia and noncardia adenocarcinomas, both intestinal and diffuse types (14). β-carotene was also strongly inversely associated with both cardia and noncardia gastric cancer risk, especially the intestinal type.

As for associations between macronutrients and risk of adenocarcinomas of the esophagus and/or gastric cardia, several recent studies suggest that dietary fat (15–17), protein (18), and cholesterol (18) are associated with an increased risk, whereas dietary fiber is associated with a reduced risk (5,

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[3] The abbreviations used are: GERD, gastroesophageal reflux disease; FHCRC, Fred Hutchinson Cancer Research Center; OR, odds ratio; CI, confidence interval.

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15–17). Vegetables and/or fruit have been inversely associated with risk of these cancers in several studies (5, 17–19).

Given the dietary associations observed in previous studies of esophageal and gastric cancers, one of the primary aims of our multicenter, collaborative population-based study of four tumor types was to collect extensive dietary data, to perform detailed analyses relating nutrient intake and dietary patterns/behaviors to the risk of these four cancers. This paper presents the nutrient analyses of this study.

Subjects and Methods

Study Populations. A detailed description of the methods used in this study is available elsewhere (10). Briefly, this multicenter case-control study was conducted in three geographic areas of the United States with population-based tumor registries: the state of Connecticut, a 15-county area of New Jersey, and a three-county area of western Washington state. The goal of the collaborative project was to identify, recruit, and interview four population-based case groups of approximately equal size including subjects with newly diagnosed esophageal adenocarcinoma, gastric cardia adenocarcinoma, esophageal squamous cell carcinoma, or noncardia gastric adenocarcinoma. Institutional review board approval was obtained from all of the participating centers.

Potentially eligible cases were English-speaking men and women who were 30–79 years of age and who were diagnosed from 1993 to early 1995. We attempted to recruit all of the subjects diagnosed with adenocarcinomas of the esophagus and gastric cardia (target cases of primary interest in this etiological study), and a frequency-matched random sample of persons with esophageal squamous cell carcinoma and noncardia gastric adenocarcinoma (comparison case groups). All of the cases were identified by rapid-reporting systems in each of the three areas. Pathology reports were obtained for all potentially eligible case patients, and final determination of eligibility was based on a systematic review of slides and medical records by the two study pathologists (A. B. W., H. R.).

Population-based controls were frequency matched to the expected distribution of target cases by 5-year age group, sex, and geographic area (study site). Controls, ages 30–64, were identified by Waksberg's random digit dialing method (20); those who were 65–79 years of age were identified by Health Care Financing Administration rosters.

Data Collection. Face-to-face interviews were obtained for 80.6% of eligible target cases (adenocarcinomas of the esophagus or gastric cardia), 74.1% of comparison case subjects (esophageal squamous cell carcinomas and noncardia gastric adenocarcinoma), and 70.2% of eligible controls. Despite our efforts to rapidly identify and interview cases (mean time between diagnosis and case interview, 3.7 months), proxy interviews were required for 29.6% of target cases, 32.2% of comparison cases, and 3.4% of controls.

After obtaining written informed consent, trained interviewers administered a structured questionnaire that contained questions on demographics, tobacco and alcohol, other beverage use (*e.g.*, coffee, tea), medical history, use of medications, and occupational history. Dietary and nutrient data were obtained as follows. First, subjects were asked to report their usual frequency of consumption of selected foods in the period 3–5 years before diagnosis or interview. The food-frequency questionnaire was based on one that was developed and previously validated (21) by investigators at the FHCRC. Subjects were asked to report how many times they consumed 104 different foods per day, per week, per month, or per year. The FHCRC questionnaire was modified slightly, in that foods with variable nitrite levels that were grouped together in the original questionnaire were asked about separately in this investigation. As a typical example, we specifically inquired about nonsmoked chicken or turkey as a lunch meat (low nitrite) *versus* smoked turkey as a lunch meat (high nitrite). Data from the food frequency questionnaire were entered and verified and then sent to the FHCRC for processing. Data were linked with the University of Minnesota, Nutrition Coding Center Nutrient Data System, for estimation of nutrient intake. Nitrite intake was estimated using a nitrite database developed for use in other epidemiological studies of gastric cancer (22).

In addition to the food frequency questionnaire, we asked several questions about general dietary behaviors and behaviors thought to be related to reflux, such as the frequency and timing of meals. Subjects were also asked to report whether they ever took any multivitamin supplements at least once a week for 6 months or longer, and, if so, the type of supplement and number of tablets taken per day or per week were queried. Finally, subjects were asked if they had ever taken supplements of vitamin A, vitamin C, vitamin E, iron, or calcium/Tums at least once a week for 6 months or longer. If yes, the number of tablets per day or week, and units per tablet were also queried.

Blood samples were obtained on a subsample of study participants (*e.g.*, 24% of target cases and 33% of controls) for evaluation of *H. pylori* infection status as described elsewhere (12). However, this variable was not considered in the present analysis because of the amount of missing data for this exposure.

Statistical Analysis. Unconditional logistic regression was used to calculate ORs, as an estimate of the relative risk, and corresponding 95% CIs for each of the four tumor types compared independently to the controls in relation to nutrient intake. All of the nutrient models included the following covariates (continuous unless otherwise specified): site (Connecticut/New Jersey/Washington); age; sex (male/female); race (white/other); proxy status (proxy/nonproxy); usual adult body mass index; income (ordered categorical variable, six levels); education (ordered categorical, seven levels); average number of cigarettes smoked per day; and years of consuming beer, wine, and liquor (each separately). Energy adjustment was done in two ways: using the standard multivariate approach and the residual method. Results were similar; therefore, those shown are based on the standard multivariate approach. Data were first analyzed separately for each gender group. Gender-specific results were nearly identical; therefore, the results shown are based on men and women combined. We also ran the nutrient analyses restricting the data to subjects who were interviewed directly (excluding all of the dietary data obtained in proxy interviews); again, the results were nearly identical; therefore, those shown are based on the total subject population. All of the tests of significance were two-sided, with a P of 0.05 considered statistically significant.

Several of the nutrients of interest (*e.g.*, vitamin C, β-carotene, folate, fiber, vegetable protein) are concentrated in plant-derived foods, whereas others (*e.g.*, saturated fat, cholesterol, vitamin B12, animal protein) are primarily in foods of animal origin. To see which of the nutrients had the greatest impact on the fit of the model predicting the risk of adenocarcinomas of the esophagus and gastric cardia, taking into account other related nutrients and covariates, we used likelihood ratio tests as follows. Logistic regression models were constructed with a group of plant-based nutrients of interest and other covariates as the independent variables and case-control status as the dependent variable. Each nutrient was removed

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Table 1 Demographic characteristics of study population from multicenter, collaborative study of esophageal and gastric cancer

	Controls $n = 687$	Case groups			
		Esophageal adenocarcinoma $n = 282$	Gastric cardia adenocarcinoma $n = 255$	Esophageal squamous cell carcinoma $n = 206$	Noncardia gastric cancer $n = 352$
Site					
New Jersey	332	137	112	93	170
Connecticut	204	77	79	78	111
Washington	151	68	64	35	71
Sex (% male)	79.9	83.3	85.1	80.6	69.3
Race (% nonwhite)	4.9	0.7	1.2	20.9	8.5
Mean age	61.8	63.7	62.5	64.8	65.9
Mean usual adult BMI[a]	25.4	26.8	26.5	24.3	25.3
Mean kcal/day	1930	1990	2030	1880	1970

[a] BMI, body mass index.

one at a time from the model, and the resulting change in the deviance between the two models (likelihood ratio statistic) was estimated. Next, we performed a similar analysis of selected nutrients concentrated in animal products. Finally, we ran multivariate models that incorporated all of the nutrients of interest simultaneously, along with the confounding variables.

Results

A total of 1839 persons were interviewed for this study. The dietary portion of the questionnaire was not completed for 34 subjects who had abbreviated interviews because of serious illness. Persons with implausible energy intake estimates [<600 kcal/day ($n = 20$) or >5000 kcal/day ($n = 3$)] were excluded from further analysis. This left a total of 1782 persons for the dietary analysis, consisting of 687 controls, 282 cases with esophageal adenocarcinoma, 255 with gastric cardia adenocarcinoma, 206 with esophageal squamous cell carcinoma, and 352 with noncardia gastric adenocarcinoma.

Table 1 shows selected demographic characteristics of the participants; additional characteristics of this population have been reported previously (10). Compared with esophageal squamous cell carcinoma cases, esophageal adenocarcinoma cases were more likely to be Caucasian and tended to be heavier. Cases with gastric cardia adenocarcinoma were similar to cases with noncardia gastric adenocarcinoma, except for the lower proportion of women with cardia (14.9%) than noncardia gastric tumors (30.7%) and the lower proportion of nonwhites with cardia (1.2%) than noncardia gastric tumors (8.5%). Attempts were made to match comparison cases to target cases on sex (Washington and New Jersey) and race (New Jersey); therefore, the demographic differences between the case populations may be underestimated.

Tables 2 and 3 show the adjusted ORs for the various case groups compared with the controls for selected nutrients from foods. To simplify the presentation of associations for multiple nutrients and the four case groups, we present only results from modeling each nutrient as a continuous variable. ORs are scaled based on the interquartile range for each nutrient and, thus, show the risk comparing the 75th percentile of intake for each nutrient with the 25th percentile.

Intake of total fat (OR, 2.18; 95% CI, 1.27–3.76), saturated fat (OR, 2.34; 95% CI, 1.55–3.54), and percentage of kilocalories from fat (OR, 1.57; 95% CI, 1.22–2.02) showed significant positive associations with the risk of esophageal adenocarcinoma (Table 2). Saturated fat also showed significant positive associations with esophageal squamous cell carcinoma (OR, 2.16; 95% CI, 1.30–3.58) and noncardia gastric cancer (OR, 1.51; 95% CI, 1.04–2.19). In contrast, polyunsaturated fat was inversely associated with the risk of all four tumor types, although significant only for esophageal squamous cell cancer (OR, 0.41; 95% CI, 0.25–0.66), and for noncardia gastric cancer (OR, 0.66; 95% CI, 0.47–0.93). Increased consumption of dietary fiber, whether expressed as total fiber, insoluble fiber, soluble fiber, or fiber/kcal, was associated with a significantly lower risk of all four tumor types. Dietary carbohydrate also was associated with a lower risk of all tumor types, although the association was significant only for esophageal adenocarcinoma (OR, 0.34; 95% CI, 0.20–0.58). Increased starch intake showed a significant increase in the risk of both types of gastric cancer but not of esophageal cancer of either histology. Increased intake of total protein, animal protein, and cholesterol was significantly associated with the risk of all tumor types, whereas vegetable protein was inversely associated with risk (although not significant for gastric cardia adenocarcinoma). Dietary sodium (from foods) was positively associated only with risk of noncardia gastric cancer (OR, 1.46; 95% CI, 1.00–2.15).

Dietary intake of β-carotene, folate, vitamin C, and vitamin B6 from foods was inversely associated with the risk of all four tumor types (Table 3). Dietary vitamin E was also inversely associated with risk; this effect was significant for esophageal squamous cell carcinoma (OR, 0.37; 95% CI, 0.22–0.60) and noncardia gastric cancer (OR, 0.71; 95% CI, 0.54–0.94) and borderline significant for adenocarcinomas of the esophagus and gastric cardia. There was a significant positive association between dietary vitamin B12 and the risk of all tumor types.

For this study, vitamin supplement use was defined as self-reported use at least once a week for 6 months or longer. There was no association between use of multivitamin supplements and risk of any tumor type (Table 4). Use of vitamin C supplements was associated with a significantly lower risk of all four tumor types in unadjusted analyses (ORs ranged from 0.42 for esophageal squamous cell carcinoma to 0.70 for esophageal adenocarcinoma; data not shown), but with adjustment for potential confounders, only the association with noncardia gastric cancer remained significant (OR, 0.60; 95% CI, 0.41–0.88). Use of supplemental vitamin E was associated with a lower risk of esophageal squamous cell carcinoma in unadjusted analyses (OR, 0.39; 95% CI, 0.23–0.68), but this association was attenuated and no longer significant after adjustment (OR, 0.66; 95% CI, 0.33–1.32). Cases with adeno-

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Table 2 Macronutrient intake and risk of esophageal and gastric cancer, from United States multicenter, population-based study

Results are adjusted[a] ORs and 95% CIs, comparing the 75th percentile of intake to the 25th percentile of intake for each nutrient.

	Esophageal adenocarcinoma *vs.* control	Gastric cardia adenocarcinoma *vs.* control	Esophageal squamous cell carcinoma *vs.* control	Noncardia gastric cancer *vs.* control
Energy	1.12 (0.91–1.38)	1.15 (0.94–1.41)	0.77 (0.59–1.01)	1.11 (0.92–1.34)
Total fat	2.18 (1.27–3.76)	0.99 (0.59–1.66)	0.98 (0.52–1.86)	1.08 (0.67–1.74)
Saturated fat	2.34 (1.55–3.54)	1.19 (0.80–1.77)	2.16 (1.30–3.58)	1.51 (1.04–2.19)
Polyunsaturated fat	0.86 (0.59–1.24)	0.86 (0.60–1.22)	0.41 (0.25–0.66)	0.66 (0.47–0.93)
% kcal from fat	1.57 (1.22–2.02)	1.07 (0.84–1.35)	1.20 (0.90–1.60)	1.13 (0.91–1.40)
Total fiber	0.28 (0.19–0.40)	0.43 (0.30–0.61)	0.24 (0.14–0.38)	0.38 (0.28–0.53)
Insoluble fiber	0.28 (0.19–0.41)	0.45 (0.32–0.64)	0.24 (0.15–0.38)	0.40 (0.29–0.55)
Soluble fiber	0.30 (0.21–0.43)	0.42 (0.30–0.59)	0.27 (0.16–0.43)	0.40 (0.29–0.55)
Fiber per kcal	0.39 (0.29–0.52)	0.51 (0.39–0.66)	0.32 (0.22–0.46)	0.51 (0.40–0.64)
Starch	1.12 (0.80–1.59)	1.61 (1.14–2.28)	1.14 (0.73–1.78)	2.07 (1.51–2.83)
Carbohydrate	0.34 (0.20–0.58)	0.70 (0.42–1.17)	0.68 (0.37–1.25)	0.64 (0.40–1.01)
Total protein	1.49 (1.02–2.18)	1.64 (1.11–2.42)	1.75 (1.07–2.88)	1.52 (1.08–2.15)
Animal protein	1.79 (1.33–2.41)	1.60 (1.19–2.15)	2.14 (1.47–3.12)	1.58 (1.22–2.06)
Vegetable protein	0.39 (0.27–0.58)	0.75 (0.53–1.07)	0.34 (0.21–0.56)	0.63 (0.45–0.87)
Cholesterol	1.74 (1.36–2.23)	1.50 (1.19–1.90)	1.63 (1.22–2.18)	1.68 (1.35–2.09)
Calcium	1.00 (0.77–1.30)	1.04 (0.79–1.37)	1.26 (0.91–1.75)	0.90 (0.70–1.16)
Sodium	0.93 (0.61–1.41)	1.31 (0.86–2.00)	1.06 (0.63–1.80)	1.46 (1.00–2.15)

[a] Adjusted for sex; site (Connecticut, Washington, New Jersey); age; race (white *versus* other); proxy status; income; education; usual body mass index; cigarettes/day; years of consuming beer, wine, and liquor (each); and energy intake. (Energy, percentage of kilocalories from fat, and fiber per kilocalorie not further adjusted for energy.)

Table 3 Micronutrient intake from foods and risk of esophageal and gastric cancer, from United States multicenter, population-based study

Results are adjusted[a] ORs and 95% CIs, comparing the 75th percentile of intake to the 25th percentile of intake for each nutrient.

	Esophageal adenocarcinoma *vs.* control	Gastric cardia adenocarcinoma *vs.* control	Esophageal squamous cell carcinoma *vs.* control	Noncardia gastric cancer *vs.* control
Vitamin A	0.47 (0.34–0.66)	0.45 (0.32–0.63)	0.53 (0.36–0.79)	0.60 (0.46–0.79)
Beta-carotene	0.43 (0.32–0.59)	0.46 (0.34–0.62)	0.43 (0.29–0.63)	0.58 (0.46–0.75)
Retinol	1.07 (0.84–1.35)	0.99 (0.77–1.28)	1.15 (0.88–1.50)	1.05 (0.85–1.28)
Vitamin D	1.10 (0.86–1.40)	1.05 (0.81–1.36)	1.00 (0.74–1.36)	0.92 (0.72–1.16)
Vitamin E	0.73 (0.54–1.00)	0.75 (0.55–1.02)	0.37 (0.22–0.60)	0.71 (0.54–0.94)
Thiamin	0.73 (0.50–1.07)	1.03 (0.71–1.50)	0.78 (0.46–1.30)	1.20 (0.85–1.70)
Riboflavin	1.11 (0.82–1.52)	1.20 (0.86–1.66)	1.26 (0.84–1.89)	1.19 (0.89–1.59)
Niacin	1.07 (0.77–1.48)	1.12 (0.82–1.54)	0.74 (0.48–1.16)	1.13 (0.84–1.52)
Folate	0.48 (0.36–0.66)	0.73 (0.55–0.97)	0.58 (0.39–0.86)	0.67 (0.51–0.88)
Vitamin B6	0.53 (0.38–0.73)	0.65 (0.47–0.88)	0.45 (0.30–0.69)	0.59 (0.45–0.79)
Vitamin B12	1.39 (1.10–1.76)	1.27 (1.01–1.60)	1.51 (1.15–2.00)	1.38 (1.13–1.68)
Vitamin C	0.45 (0.33–0.61)	0.64 (0.49–0.84)	0.53 (0.36–0.79)	0.59 (0.45–0.76)
Iron	0.79 (0.57–1.09)	1.03 (0.75–1.40)	0.75 (0.49–1.16)	1.13 (0.85–1.50)
Zinc	1.23 (0.92–1.65)	1.28 (0.95–1.72)	1.40 (0.95–2.06)	1.22 (0.92–1.60)

[a] Adjusted for sex; site (Connecticut, Washington, New Jersey); age; race (white *versus* other); proxy status; income; education; usual body mass index; cigarettes/day; years of consuming beer, wine, and liquor (each); and energy intake.

carcinoma of the esophagus and gastric cardia were significantly more likely than controls to report use of calcium/Tums (ORs, 1.79 and 1.74, respectively; Table 4). For subjects who reported using nutrient supplements, efforts to obtain specific dosage information were complicated by the considerable amount of missing data, attributable to inadequate recall of doses by many subjects. As a result, we did not attempt to quantify the amount of nutrient supplements or total intake of a given nutrient (diet plus supplement).

Table 5 shows analyses of the main effect of nitrite intake, with and without adjustment for confounders and for sodium intake from foods. On the basis of models adjusted for key covariates except sodium, dietary nitrite was associated with risk of noncardia gastric cancer (OR, 1.64; 95% CI, 1.30–2.07), but not with the risk of the other tumor types. The association between nitrite and the risk of noncardia gastric cancer was unaltered with additional adjustment for dietary sodium (OR, 1.65). In contrast, the borderline association of dietary sodium with the risk of

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Table 4 Supplemental nutrient intake and risk of esophageal and gastric cancer, from United States multicenter, population-based study

Results show adjusted[a] ORs, 95% CIs, and proportion of subjects who took the supplement at least once a week for 6 months or longer.

	Controls	Esophageal adenocarcinoma	Gastric cardia adenocarcinoma	Esophageal squamous cell carcinoma	Noncardia gastric cancer
Any multivitamin		1.07 (0.76–1.51)	0.87 (0.61–1.23)	1.19 (0.77–1.83)	1.15 (0.84–1.56)
	33.9%	35.1%	30.2%	37.4%	39.2%
One-A-Day Type		1.24 (0.86–1.79)	1.18 (0.82–1.71)	1.22 (0.76–1.96)	1.13 (0.81–1.59)
	25.0%	25.5%	25.1%	28.2%	29.0%
Theragran Type		0.81 (0.45–1.48)	0.60 (0.31–1.16)	1.19 (0.57–2.47)	1.28 (0.77–2.11)
	8.3%	8.5%	5.9%	8.3%	10.5%
Stress Vitamin Type		0.75 (0.25–2.27)	0.34 (0.08–1.55)	1.30 (0.33–5.13)	1.39 (0.56–3.46)
	2.5%	2.1%	0.8%	2.4%	2.3%
Any single nutrient supplement		0.90 (0.63–1.28)	0.80 (0.55–1.14)	0.66 (0.40–1.08)	0.77 (0.55–1.07)
	32.6%	28.0%	25.1%	19.9%	28.4%
Vitamin A		0.60 (0.24–1.52)	0.87 (0.37–2.04)	0.64 (0.19–2.16)	0.40 (0.15–1.05)
	4.5%	3.2%	3.5%	1.9%	2.3%
Vitamin C		0.75 (0.51–1.11)	0.71 (0.48–1.07)	0.71 (0.41–1.22)	0.60 (0.41–0.88)
	25.6%	19.5%	18.4%	12.6%	17.6%
Vitamin E		0.75 (0.47–1.20)	0.86 (0.54–1.37)	0.66 (0.33–1.32)	0.88 (0.58–1.33)
	16.6%	13.8%	13.3%	7.3%	14.5%
Iron		1.32 (0.45–3.85)	0.48 (0.11–2.10)	1.15 (0.34–3.90)	1.35 (0.54–3.38)
	2.0%	2.1%	1.2%	3.9%	3.7%
Calcium/Tums		1.79 (1.08–2.98)	1.74 (1.04–2.93)	0.68 (0.29–1.60)	0.87 (0.51–1.49)
	9.5%	12.8%	12.5%	6.3%	8.8%

[a] Adjusted for sex; site (Connecticut, Washington, New Jersey); age; race (white *versus* other); proxy status; income; education; usual body mass index; cigarettes/day, years of consuming beer, wine, and liquor (each); and energy intake.

Table 5 Dietary nitrite and risk of esophageal and gastric cancer, from United States multicenter, population-based study

Results are ORs and 95% CIs, comparing the 75th percentile of intake to the 25th percentile of intake.

	Esophageal adenocarcinoma *vs.* control	Gastric cardia adenocarcinoma *vs.* control	Esophageal squamous cell carcinoma *vs.* control	Noncardia gastric cancer *vs.* control
Nitrite	1.17 (1.00–1.36)	1.18 (1.01–1.38)	1.15 (0.97–1.36)	1.31 (1.14–1.51)
Nitrite adjusted for covariates[a]	1.02 (0.80–1.30)	1.12 (0.87–1.44)	1.12 (0.84–1.51)	1.64 (1.30–2.07)
Nitrite adjusted for sodium and covariates	1.05 (0.80–1.38)	1.05 (0.79–1.40)	1.13 (0.82–1.56)	1.65 (1.26–2.16)
Sodium adjusted for nitrite and covariates	0.90 (0.56–1.44)	1.26 (0.78–2.03)	0.97 (0.54–1.73)	0.97 (0.54–1.53)

[a] Adjusted for sex; site (Connecticut, Washington, New Jersey); age; race (white *versus* other); proxy status; income; education; usual body mass index; cigarettes/day; years of consuming beer, wine, and liquor (each); and energy intake.

noncardia gastric cancer (Table 2; OR, 1.46; 95% CI, 1.00–2.15) was no longer present after adjustment for nitrite and other covariates (Table 5; OR, 0.97; 95% CI, 0.54- 1.53).

Because nitrosation in the stomach is inhibited by vitamin C, we investigated the joint effects of nitrite and vitamin C from foods on cancer risk by stratifying the study population into high *versus* low intake of each, with cutpoints set at the median intake levels in the control population. For each tumor type, persons with high nitrite and low vitamin C intake were at greatest risk (Table 6), with significant ORs ranging from 2.18 (gastric cardia carcinoma) to 3.92 (esophageal squamous cell carcinoma), compared with persons with low nitrite and high vitamin C intake. The test for an interaction between nitrite and vitamin C was not significant for any of the four case groups.

Likelihood ratio tests were used to see which of the nutrients had the greatest impact on the fit of the model predicting the risk of adenocarcinomas of the esophagus and gastric cardia, taking into account other related nutrients and covariates. In models that included the plant-based nutrients and covariates, dropping total fiber from the model produced the greatest impact on the model fit (likelihood ratio statistic, 16.1 with 1 *df*). In models that included the nutrients concentrated in animal products and covariates, dropping cholesterol from the model produced the greatest impact on the model fit (likelihood ratio statistic, 7.8 with 1 *df*). In models that included both plant-based nutrients and those concentrated in animal products, along with covariates, the likelihood ratio statistics comparing the full model to a model without the nutrient of interest were as follows (all 1 *df*): fiber, 11.8; β-carotene, 6.8; vegetable protein, 6.7; animal protein, 3.3; cholesterol, 1.5; all other nutrients, <1.5. Thus, dietary fiber had the largest impact on the fit of models predicting risk of adenocarcinomas of the esophagus and gastric cardia, after adjusting for the other nutrients and covariates of interest.

Because GERD is an important risk factor for esophageal adenocarcinoma, it could be argued that patients with GERD might have altered their diets some years in the past so as to avoid exacerbating the symptoms of GERD. For example, patients with GERD could have avoided high-fiber foods that might be construed as being irritating to the esophagus, or could

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Table 6 Interactive effects of dietary nitrite and vitamin C on risk of esophageal and gastric cancer, from United States multicenter, population-based study

Results are ORs and 95% CIs.

	Esophageal adenocarcinoma *vs.* control	Gastric cardia adenocarcinoma *vs.* control	Esophageal squamous cell carcinoma *vs.* control	Noncardia gastric cancer *vs.* control
High C, low nitrite[a]	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
High C, high nitrite	1.65 (1.05–2.61)	1.40 (0.88–2.22)	1.50 (0.84–2.67)	2.10 (1.36–3.25)
Low C, low nitrite	1.76 (1.12–2.78)	1.52 (0.97–2.39)	2.51 (1.46–4.32)	2.25 (1.46–3.47)
Low C, high nitrite	2.72 (1.73–4.27)	2.18 (1.38–3.43)	3.92 (2.28–6.74)	2.95 (1.90–4.59)

[a] High, above the median intake level in the control population; low, below the median intake level in the control population.

have avoided high-fat foods, which are known to exacerbate reflux. This scenario, if true, could produce an artifactual inverse association between nutrients like fiber and subsequent cancer risk, or could attenuate the association for nutrients like fat that may increase risk. To examine this possibility, we conducted additional stratified analyses, focusing on persons who did not report having any GERD symptoms (*e.g.,* 40% of cases with adenocarcinoma of the esophagus and 53% of controls reported having no GERD symptoms; that is, no heartburn or acid regurgitation). The inverse associations for dietary fiber remained statistically significant in this restricted analysis for all four case groups, with almost no impact on the magnitude of the associations (*e.g.,* fiber OR, 0.24; 95% CI, 0.13- 0.45 for esophageal adenocarcinoma cases without reflux symptoms, compared with 0.28; 95% CI, 0.17- 0.46 for those with reflux symptoms). In the restricted analysis, total fat remained a statistically significant risk factor for esophageal adenocarcinoma but not for other tumor types. However, the observed association between total fat intake and esophageal adenocarcinoma was more pronounced among persons without reflux symptoms (OR, 3.21; 95% CI, 1.33- 8.00) as compared with those with reflux symptoms (OR, 1.93; 95% CI, 0.95- 4.04).

Discussion

In this population-based case-control study of adenocarcinomas of the esophagus and gastric cardia, we found a decreased risk associated with higher intake of several nutrients found primarily in plant-based foods, and an elevated risk associated with higher intake of several nutrients found mainly in foods of animal origin. Because these nutrients reflect the overall dietary pattern and can be highly correlated, it is difficult to implicate the specific nutrients or their combinations that are responsible for the protective effects. With the use of multivariate statistical models, we were able to determine that dietary fiber, in particular, was strongly related to a reduced risk of adenocarcinomas of the esophagus and gastric cardia. A protective effect of dietary fiber on esophageal adenocarcinoma has been reported previously in a population-based case-control study (5) and in hospital-based case-control studies (15–17). Although the protective mechanism of fiber is unclear, it may act by limiting the development of hiatal hernia (23), or by a mechanical cleansing or clearance action that could facilitate the removal of carcinogens at the epithelial surface (5) or promote the sloughing of damaged epithelial cells.

Although fiber was inversely associated with the risk of all four cancer types in our study, total fat intake was significantly associated only with the risk of esophageal adenocarcinoma (OR, 2.18). For saturated fat, higher intake was significantly associated with the risk of all of the cancer types except gastric cardia tumors. In previous studies, the risk of adenocarcinomas of the esophagus and gastric cardia has been linked to high-fat diets (15–17). The effect that we observed for high-fat diets was not mediated through adiposity, a strong risk factor for these tumors (3), because our estimates were all adjusted for usual adult body mass index. Also, the unadjusted association for total fat was virtually identical to the association adjusted only for body mass index. Cases, particularly those with GERD, may have reduced fat intake to avoid exacerbating reflux symptoms. If so, the true magnitude of the association for dietary fat may be greater than observed in our study. Support for this notion was evident by restricting the analysis for dietary fat to cases of esophageal adenocarcinoma and controls who reported no GERD symptoms, because the OR in this subgroup increased to 3.21.

Greater consumption of starch in the diet was associated with a significantly increased risk of cardia and noncardia gastric cancers. As reviewed elsewhere (24), several studies from around the world have linked high-starch diets to an increased risk of stomach cancer. The mechanism of action is unclear but may involve physical irritation of gastric mucosa or promotion of acid-catalyzed nitrosation by the lowering of gastric pH (25). It is possible, however, that the association is related in part to micronutrient deficiencies that often accompany high-starch diets. When the association between starch intake and risk (Table 2) was further adjusted for the intake of folate, vitamin C, β-carotene, vitamin B6, and total fiber, the association increased from 1.61 to 2.20 (95% CI, 1.45–3.31) for gastric cardia, and from 2.07 to 3.17 (95% CI, 2.19–4.60) for noncardia gastric cancer.

Higher intake of nitrite (Table 5) and sodium (Table 2) were each associated with an increased risk of noncardia gastric cancer when modeled separately in our study. There is a considerable body of epidemiological and experimental data indicating that high-salt diets may increase the risk of stomach cancer (24). Salt itself is not carcinogenic but is thought to damage the protective mucosal layer in the stomach, resulting in an inflammatory regenerative response, increased DNA synthesis, and cell proliferation (24). High-salt diets have been shown to induce parietal cell loss and gastric epithelial hyperplasia and to enhance *H. pylori* colonization in rodent models of gastric carcinogenesis (26). However, as discussed by Hill (27), not all epidemiological studies have observed a relation between salt and gastric cancer, probably because the association is mainly seen when salt is ingested in circumstances in which *N*-nitroso compounds are involved as well. Most studies examining nitrite intake or smoked meat have shown an increased risk of gastric cancer at higher levels of consumption. In our analyses, when both nitrite and salt were modeled simultaneously against risk of noncardia gastric cancer (with adjustment for covariates), only nitrite intake remained significantly associated with noncardia gastric cancer risk (Table 5), consistent with the results of others (22).

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Epidemiological evidence that vitamin C intake reduces the risk of gastric cancer is fairly robust; 12 of 13 case-control studies reviewed recently found a decreased risk of stomach cancer with higher intakes of dietary vitamin C (24). In our data, both dietary and supplemental vitamin C were significantly inversely associated with the risk of noncardia gastric adenocarcinoma. Vitamin C is thought to inhibit the intragastric formation of *N*-nitroso compounds, which may explain our finding that persons with high nitrite and low vitamin C consumption were at particularly increased risk. Also, infection with *H. pylori* depletes gastric juice ascorbic acid (28, 29), and higher serum ascorbic acid has been associated with a decreased risk of the progression of precancerous lesions to gastric cancer in a population with a high prevalence of infection (30). Supplemental vitamin C (1 g twice a day) also resulted in a statistically significant increase in the rate of regression of gastric precancerous lesions in a randomized trial in Colombia (31). A large intervention trial in Linxian County, China, however, has failed thus far to see a reduction in the incidence of esophageal or gastric cancer in persons given supplemental vitamin C (120 mg/day) along with molybdenum (30 μg/day) for 5.25 years (32), which suggests that the protective effect of vitamin C, if real, occurs early in the carcinogenic process.

In the Linxian trial, the combination of vitamin E, β-carotene, and selenium reduced the incidence of gastric cancer by 21% and esophageal cancer by 4%, in line with our findings of significant inverse associations for dietary β-carotene (all four of the tumor types) and vitamin E ($P \leq 0.05$, all of the types except gastric cardia cancer). Other observational studies also report that these antioxidant nutrients are inversely associated with risk (13, 14), and recent literature suggests that vitamin E and β-carotene concentrations in the stomach are affected by *H. pylori*-associated gastric histological changes (33). Alternatively, selenium may have been responsible for the lowered risks observed with the combination intervention in the Linxian County trial. This is consistent with the finding that dietary selenium, but not β-carotene or vitamins C and E, was inversely associated with cell cycle predictors of neoplastic progression in patients with Barrett's esophagus (34).

Cases with adenocarcinoma of the esophagus and gastric cardia were almost twice as likely as controls to report consuming supplemental calcium/Tums. Calcium from foods (primarily dairy products) was not associated with the risk of any of the tumor types. The greater use of calcium/Tums in the cases was as expected, given the excess risk of these cancers associated with gastroesophageal reflux in our study (8). When we stratified the population into those with and without GERD symptoms, the use of supplemental calcium was significantly associated with the risk of esophageal adenocarcinoma only in persons who reported GERD symptoms [OR for those with GERD, 2.15 (95% CI, 1.12–4.12) *versus* 1.51 (95% CI, 0.87–2.62) for those without GERD]. The excess risk observed in the two target-case groups but not in the comparison-case groups suggests that the supplement data were reported reliably.

There has been considerable interest in dietary folate, along with vitamin B6 and vitamin B12, as potential preventive agents in colorectal and possibly other cancers. These nutrients, and folate in particular, may influence both methylation of DNA and the available nucleotide pool for DNA replication and repair (35). For all of the tumor types in our study, we observed significant protective effects for dietary folate and vitamin B6. Vitamin B12, in contrast, was positively associated with the risk of all cancer types. Because dietary vitamin B12 is derived exclusively from foods of animal origin, it seems likely that vitamin B12 is simply a marker for consumption of animal protein.

Esophageal adenocarcinoma generally arises from Barrett's epithelium, a premalignant lesion that can develop in patients with GERD (36). For patients with GERD and Barrett's esophagus, interventions are needed to reduce the risk of malignant transformation. Our results suggest that dietary regimens should be explored, especially diets rich in fruits, vegetables, and fiber, and low in animal protein and fat, along with weight loss in obese patients (3), smoking cessation (10), and the use of nonsteroidal anti-inflammatory drugs (11).

Although this study is one of the largest to date to evaluate the relation of nutrients to esophageal and gastric cardia adenocarcinomas, it has some limitations. These cancers have high case-fatality rates. Despite our efforts to identify and interview cases rapidly, proxy interviews were required for ~30% of cases. Because of the large sample size, we were able to perform analyses restricted to subjects who were interviewed directly, and the results were essentially unchanged.

Another possible limitation inherent in case-control study designs is the possibility that cases may have recalled their diet and supplement-taking practices differently after a cancer diagnosis. While recall bias may have influenced our results, one would expect the bias to operate similarly in all four of the case groups; therefore, it would not explain many of the associations that were specific to a certain tumor type, such as the effect of fat intake on esophageal adenocarcinoma, the effect of starch on both gastric cancer subsites, and the effect of nitrite on noncardia gastric cancer. A related concern is that patients may have altered their diets as a result of reflux symptoms, so that some associations may be a consequence rather than a cause of the disease. When we restricted our analysis to persons who reported no reflux symptoms, the diet-related risks persisted and some associations (*e.g.*, dietary fat) became even more pronounced.

Perhaps the major concern in interpreting our results is that some of the associations may not be attributable to specific nutrients *per se*, but rather may reflect dietary patterns. For example, the observed interaction between nitrite and vitamin C may simply reflect a diet characterized by the high consumption of processed red meats and a low intake of fruits and vegetables. We are completing a separate analysis of specific foods, food groups, and dietary behaviors as they relate to the risk of these cancers.

An overall goal of this population-based case-control study was to identify possible reasons for the disparate time trends in incidence for these four tumor types. This would require evidence that the magnitude or direction of associations between risk factors and adenocarcinomas of the esophagus and gastric cardia were notably different from the associations with esophageal squamous cell cancers and noncardia gastric cancers. As detailed above, the majority of the associations with nutrient intake that we observed were similar across the four tumor types. Total fat intake was associated only with adenocarcinoma of the esophagus, and fat content of the United States food supply has increased 38% between 1909–14 and 1988 (37). However, this gain is attributable primarily to an increase in fat from vegetable sources (salad and cooking oils and margarines). This suggests that trends in the intake of fat or other nutrients are unlikely to explain a major portion of the disparate trends in incidence for these tumor types.

In conclusion, our results suggest that several nutrients found in plant-based diets lower the risk of adenocarcinomas of the esophagus and gastric cardia, esophageal squamous cell carcinoma, and noncardia gastric adenocarcinoma. Also, sev-

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eral nutrients concentrated in foods of animal origin elevate the risk of these cancers. These results have implications for strategies aimed at preventing all of these cancers, but especially for adenocarcinomas of the esophagus and gastric cardia, given their increasing incidence rates.

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