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Food group intake and risk of subtypes of esophageal and gastric cancer

Stephanie A. Navarro Silvera[1]*, Susan T. Mayne[2], Harvey Risch[2], Marilee D. Gammon[3], Thomas L. Vaughan[4,5], Wong-Ho Chow[6], Robert Dubrow[2], Janet B. Schoenberg[7], Janet L. Stanford[4,5], A. Brian West[8], Heidrun Rotterdam[9], William J. Blot[10] and Joseph F. Fraumeni, Jr.[6]

[1]*Department of Health and Nutrition Sciences, Montclair State University, Montclair, NJ*
[2]*Yale University School of Medicine, Department of Epidemiology and Public Health, New Haven, CT*
[3]*Department of Epidemiology, University of North Carolina School of Public Health, Chapel Hill, NC*
[4]*Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, WA*
[5]*Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA*
[6]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD*
[7]*New Jersey Department of Health and Senior Services, Center for Cancer Initiatives, Trenton, NJ*
[8]*Department of Pathology, New York University, New York, NY*
[9]*Department of Pathology, Columbia University, New York, NY*
[10]*International Epidemiology Institute, Rockville, MD*

Incidence rates for adenocarcinomas of the esophagus and gastric cardia have been increasing rapidly, while rates for non-cardia gastric adenocarcinoma and esophageal squamous cell carcinoma have declined. We examined food group intake as a risk factor for subtypes of esophageal and gastric cancers in a multicenter, population-based case–control study in Connecticut, New Jersey and western Washington state. Associations between food groups and risk were estimated using adjusted odds ratios (OR), based on increasing intake of one serving per day. Total vegetable intake was associated with decreased risk of esophageal adenocarcinoma (OR = 0.85, 95% CI = 0.75, 0.96). Conversely, total meat intake was associated with increased risk of esophageal adenocarcinoma (OR = 1.43, 95% CI = 1.11, 1.83), gastric cardia adenocarcinoma (OR = 1.37, 95% CI = 1.08, 1.73) and noncardia gastric adenocarcinoma (OR = 1.39, 95% CI = 1.12, 1.71), with red meat most strongly associated with esophageal adenocarcinoma risk (OR = 2.49, 95% CI = 1.39, 4.46). Poultry was most strongly associated with gastric cardia adenocarcinoma (OR = 1.89, 95% CI = 1.15, 3.11) and noncardia gastric adenocarcinoma (OR = 1.90, 95% CI = 1.19, 3.03). High-fat dairy was associated with increased risk of both esophageal and gastric cardia adenocarcinoma. Higher intake of meats, particularly red meats, and lower intake of vegetables were associated with an increased risk of esophageal adenocarcinoma, while higher intake of meats, particularly poultry, and high-fat dairy was associated with increased risk of gastric cardia adenocarcinoma.

Key words: esophageal neoplasms; gastric neoplasms; food groups; case–control

A dramatic increase in the incidence of adenocarcinomas of the esophagus and gastric cardia has been well documented in the United States[1,2] and other developed countries[3] along with decreases in the incidence of noncardia gastric adenocarcinoma and esophageal squamous cell carcinoma.[2] In response, several population-based case–control studies, including our own, were initiated in the United States and elsewhere, particularly to identify risk factors that may have contributed to the upward trends for esophageal and gastric cardia adenocarcinoma. Results to date indicate that gastroesophageal reflux,[4–6] obesity[7–10] and cigarette smoking[10,11] are important etiologic factors, accounting for a substantial proportion of these cancers.[12]

While epidemiologic studies have pointed to a strong protective effect of fruits and vegetables on gastric and esophageal cancers without regard to subsite or histologic type,[13,14] evidence linking dietary factors to subtypes of these cancers is limited. In an earlier analysis from our population-based case–control study that evaluated the effects of nutrient intake, we found significant inverse associations between intake of nutrients found primarily in plant-based foods and the risk of esophageal and gastric cardia adenocarcinomas.[15] In another population-based study in the United States, Brown *et al.*[8] observed a significantly reduced risk of esophageal adenocarcinoma among white men reporting the highest intake of raw fruits, raw vegetables and cruciferous vegetables and Terry *et al.*[16] observed a decreased risk for esophageal adenocarcinoma associated with both fruit and vegetable consumption in a population-based study of men and women in Sweden. While Brown *et al.*[8] did not find a consistent association between consumption of meat, poultry and fish and risk of esophageal adenocarcinoma, we observed a significant positive association between intake of animal protein and risk of adenocarcinomas of the esophagus and gastric cardia.[15]

Few studies have examined the role of dairy products and risk of esophageal or gastric cardia adenocarcinoma. A case–control study by Chen *et al.*[17] reported that high milk intake was associated with a significantly increased risk of esophageal adenocarcinoma. However, 2 other case–control studies of esophageal cancer reported an inverse association with milk consumption,[18,19] although these studies did not distinguish between adenocarcinoma and squamous cell carcinoma. Likewise, few studies have investigated the effects of fiber-rich foods on these cancers. Inverse associations have been reported between dietary fiber intake and risk of adenocarcinomas of the esophagus[8,15] and gastric cardia.[15,20] For noncardia gastric cancer, the available evidence suggests a positive association with starchy grain intake, including potatoes, bread, rice and pasta.[13]

One of the primary aims of our population-based case–control study of esophageal and gastric cancers in the United States was to perform detailed analyses of dietary data. While previous analyses focused on the risk associated with nutrient intake,[15] this report describes our findings with regard to food group intake.

Material and methods

Subjects and methods

Subject recruitment and data collection methods have been described previously in detail.[11] Briefly, a multicenter, population-based, case–control study of adenocarcinomas of the esophagus and gastric cardia was conducted in 3 geographic areas of the United States with population-based tumor registries—the state of

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***Correspondence to:** Stephanie A. Navarro Silvera Department of Health and Nutrition Sciences, Montclair State University, 1 Normal Avenue, Montclair, NJ 07043, USA. Fax: +973-655-5461.
E-mail: silveras@mail.montclair.edu
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Connecticut, a 15-county area of New Jersey and a 3-county area of western Washington State. The goal of the collaborative project was to identify, recruit and interview 4 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 participating centers, and from the Connecticut Department of Public Health. In the process of case ascertainment in Connecticut, certain data used in this study were obtained from the Connecticut Tumor Registry, located in the Connecticut Department of Public Health. The authors assume full responsibility for analyses and interpretation of these data.

Only English-speaking men and women between 30 and 79 years of age who were diagnosed between 1993 and early 1995 were potentially eligible. Attempts were made to recruit all subjects diagnosed with esophageal adenocarcinoma and gastric cardia adenocarcinoma (target cases). A frequency-matched random sample of subjects diagnosed with esophageal squamous cell carcinoma and noncardia gastric adenocarcinoma (comparison case groups) was also recruited. Potential cases were identified via rapid reporting systems in each of the 3 areas. Two study pathologists systematically reviewed slides, surgery, endoscopy and radiology reports and other medical records to classify each cancer with respect to site of origin and histology.

Population-based controls were frequency-matched to the expected distribution of target cases by 5-year age group, sex (in New Jersey and Washington State), race (in New Jersey) and study site. Waksberg's random digit dialing method was utilized to identify controls aged 30–64[21]; those who were aged 65–79 years of age were identified by Health Care Financing Administration rosters.

Data collection

Interviews were obtained for 80.6% of eligible target subjects, 74.1% of comparison case subjects and 70.2% of eligible controls, with a mean time between diagnosis and case interview of 3.7 months, for a total of 1,839 individuals interviewed. Proxy interviews were utilized as needed with the closest next of kin (usually the spouse).

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. An expanded version of a food frequency questionnaire, developed and validated[22] by investigators at the Fred Hutchinson Cancer Research Center, was used to assess usual food consumption in the period 3–5 years before diagnosis (cases) or interview (controls). Subjects were asked to report how many times they consumed 104 different foods per day, per week, per month or per year. Additional questions regarding dietary behaviors and supplement use were also asked.

Of the initial 1,839 individuals interviewed, 34 subjects were seriously ill and unable to complete the dietary portion of the questionnaire and were therefore excluded from the analyses. Additional 23 persons were excluded from analysis due to implausible reporting of energy intake (<600 kcal/day, $n = 20$ or >5,000 kcal/day, $n = 3$). The dietary analyses therefore included interviews of 1,782 subjects: 687 controls, 282 cases with esophageal adenocarcinoma, 255 with gastric cardia adenocarcinoma, 206 with esophageal squamous cell carcinoma and 352 with noncardia gastric adenocarcinoma. As expected, proxy interviews were more common among cases (esophageal adenocarcinoma = 31%, adenocarcinoma of the gastric cardia = 26%, esophageal squamous cell carcinoma = 35% and noncardia gastric adenocarcinoma = 30%) than among controls (3.4%).

Food group variables were created using the food items included in the food frequency questionnaire in keeping with current USDA food group guidelines. Each of the 5 major food groups—fruits, vegetables, grains, meats and dairy—was further divided into more specific subgroups, with some foods placed in more than 1 category. Fruits were divided into citrus fruits, fruit juices and noncitrus fruits. Vegetables were categorized as deep yellow or orange, cruciferous, dark green leafy, starchy, raw, tomato products or legumes such as dry beans or peas. Dairy products were classified as high or low-fat and grains as whole or refined. Meats were categorized as poultry, fish, high-nitrite, meat alternates or red meats. Mixed dishes were assigned as partial servings based on comparison of micronutrient content of these foods to selected standards. For example, the contribution of chili with meat or beans to the meat group was determined by comparing the amount of vitamin B12 and saturated fat in this food item to that of lean ground beef. Partial contribution to food groups was rounded to the nearest quarter serving. The food groups and subgroups, including assigned serving size allocations, are detailed in Appendix.

Statistical analysis

Unadjusted comparisons of central tendencies for intake of each of the food groups and subgroups of interest were conducted using Student's *t* test to determine differences between controls and each case group separately.

Next, unconditional logistic regression was used to calculate odds ratios (OR) and corresponding 95% confidence intervals (CI) for each of the 4 tumor types compared with controls in relation to daily food group and subgroup intake. The primary predictor, number of servings of each food group or subgroup per day, was modeled as a continuous variable. All food group and subgroup models included the following covariates (continuous unless otherwise indicated): study site (Connecticut/Washington/New Jersey), age, gender, race (white/other), proxy status (proxy/nonproxy), income (ordered categorical variable, 6 levels), education (ordered categorical variable, 7 levels), usual adult body mass index (BMI), average number of cigarettes smoked per day, consumption of beer, wine and liquor (each separately) and energy intake. Additional adjustment for reflux symptoms did not materially affect the OR; so, reflux was not included as a covariate in the models reported here. When the food group analyses were limited to those subjects who were interviewed directly (excluding proxy interviews), the results were nearly identical to those for all study participants, so that the results shown are based on the total study population. Likewise, the results were similar upon stratification by gender and reflux symptoms. All tests of significance were 2-sided, with a p value of 0.05 considered statistically significant.

Certain food subgroups correlate with others; therefore, we performed additional model selection methods involving food subgroups to determine which food subgroups were consistently associated with risk of each subtype of cancer. In all methods, a cutoff p value of 0.05 was considered statistically significant for a food subgroup to be kept in the model. Three models were created using manual stepwise selection methods to determine which food subgroups were consistently associated with risk. In the first set of models, food subgroups that were found to be independently associated with cancer risk were eligible for inclusion. Stepwise selection was then performed with these subgroups, after which adjustment for demographic variables and covariables of interest was carried out to obtain an adjusted OR. The second set of models allowed all food subgroups under study to be eligible for inclusion. Again, stepwise selection was performed, after which the model was adjusted for demographic variables and covariables of interest. In the third set of models, demographic variables and covariables of interest were first entered and maintained in the model, and then selection from the full range of food subgroups was conducted for each subtype of cancer. All analyses were performed using SAS version 8.11 (SAS Institute Cary, NC).

Results

Compared to controls, subjects with adenocarcinoma of the esophagus and gastric cardia tended to be heavier and were

TABLE I – SELECTED CHARACTERISTICS OF THE STUDY SUBJECTS FROM A UNITED STATES MULTICENTER, POPULATION-BASED, CASE–CONTROL STUDY OF ESOPHAGEAL AND GASTRIC CANCER

	Controls (*N* = 687)	Esophageal adenocarcinoma (*N* = 282)	Gastric cardia adenocarcinoma (*N* = 255)	Esophageal squamous cell carcinoma (*N* = 206)	Noncardia gastric cancer (*N* = 352)
Mean age	61.8	63.7	62.5	64.8	65.9
Usual BMI	25.4	26.8	26.5	24.3	25.3
Smoking history					
% Never	35.4	22.3	21.3	10.2	29.9
% Former	42.8	50.0	47.0	42.7	44.4
% Current	21.8	27.7	31.6	47.1	25.6
Energy (kcal/day)	1930	1993	2026	1879	1967
Sex (% male)	79.9	83.3	85.1	80.5	69.3
Race (% nonwhite)	5.0	0.7	1.2	20.9	8.5
Site (%)					
New Jersey	48.3	48.6	43.9	45.2	48.3
Connecticut	29.7	27.3	31.0	37.9	31.5
Washington	22.0	24.1	25.1	17.0	20.2
Proxy status (% proxy)	3.4	30.9	25.9	34.5	30.1
Mean alcohol intake (drinks per week)					
Beer	5.9	7.4	7.4	16.2	5.6
Wine	2.3	2.1	2.8	4.0	1.5
Liquor	8.5	8.3	6.4	30.0	6.1

TABLE II – INTAKE OF FOOD GROUPS AND THEIR COMPONENT SUBGROUPS (SERVINGS/DAY) BY CANCER TYPE FROM UNITED STATES MULTICENTER, POPULATION-BASED, CASE–CONTROL STUDY: COMPARISON OF CENTRAL TENDENCIES

	Mean (90%–10%)				
	Control (*N* = 687)	Esophageal adenocarcinoma (*N* = 282)	Adenocarcinoma gastric cardia (*N* = 255)	Esophageal squamous cell carcinoma (*N* = 206)	Other gastric cancer (*N* = 352)
Fruits	2.78 (3.90)	2.42 (3.74)*	2.60 (3.95)	2.19 (3.58)*	2.76 (3.89)
Citrus	0.78 (0.67)	0.72 (0.66)	0.72 (0.57)	0.59 (0.67)*	0.77 (1.47)
Noncitrus	1.21 (3.06)	1.03 (2.65)**	1.09 (2.78)	0.89 (2.46)*	1.25 (2.17)
Fruit juices	0.78 (1.30)	0.67 (1.28)**	0.80 (1.43)	0.71 (1.14)	0.75 (1.28)
Vegetables	3.45 (3.78)	3.12 (3.50)**	3.35 (3.43)	2.91 (3.40)*	3.35 (3.63)
Cruciferous	0.38 (0.66)	0.33 (0.57)***	0.35 (0.57)	0.30 (0.54)*	0.36 (0.64)
Deep yellow	0.51 (1.00)	0.42 (0.72)*	0.46 (0.81)	0.40 (0.73)*	0.50 (0.91)
Dark green	0.41 (0.96)	0.33 (0.73)*	0.37 (0.76)	0.31 (0.71)*	0.40 (0.89)
Starchy	0.58 (0.79)	0.63 (0.85)***	0.62 (0.80)	0.57 (0.77)	0.57 (0.78)
Raw	1.40 (2.27)	1.21 (1.99)**	1.35 (2.00)	1.11 (1.93)*	1.37 (2.14)
Legumes	0.14 (0.29)	0.13 (0.27)	0.15 (0.26)	0.14 (0.29)	0.13 (0.28)
Tomato products	0.54 (0.94)	0.50 (0.84)	0.52 (0.89)	0.46 (0.87)*	0.53 (0.90)
Total fruit and vegetable	6.23 (6.71)	5.53 (6.36)*	5.96 (6.45)	5.51 (5.87)*	6.11 (6.83)
Meat	2.05 (2.22)	2.28 (2.12)*	2.32 (2.41)*	2.25 (2.19)**	2.21 (2.53)**
Fish	0.26 (0.45)	0.25 (0.41)	0.27 (0.48)	0.23 (0.40)	0.26 (0.46)
Poultry	0.49 (0.75)	0.53 (90.73)	0.57 (0.89)**	0.57 (0.95)***	0.56 (0.90)*
High nitrite	0.43 (0.90)	0.52 (0.99)**	0.50 (1.06)***	0.60 (1.04)*	0.53 (1.09)*
Red meat	0.54 (0.73)	0.66 (0.79)*	0.62 (0.72)**	0.57 (0.67)	0.58 (0.73)
Meat alternates	0.32 (0.83)	0.32 (0.83)	0.36 (0.89)	0.27 (0.68)	0.28 (0.68)***
Grains	2.78 (2.98)	2.90 (2.94)	3.01 (2.88)**	2.62 (2.68)	3.09 (3.03)*
Whole	0.72 (1.57)	0.64 (1.32)***	0.70 (1.58)	0.48 (1.29)*	0.66 (1.89)
Refined	1.69 (2.09)	1.88 (2.32)**	1.88 (2.28)**	1.82 (2.17)***	2.04 (2.51)*
Dairy	1.38 (2.26)	1.56 (2.48)**	1.55 (2.49)***	1.40 (2.25)	1.37 (2.18)
Low fat	0.28 (1.00)	0.21 (0.58)	0.22 (0.78)	0.18 (0.75)**	0.17 (0.57)*
High fat	1.10 (1.95)	1.35 (2.20)*	1.33 (2.33)*	1.20 (2.08)	1.20 (2.08)

*$p < 0.001$ *versus* controls.–**$p < 0.01$ *versus* controls.–***$p < 0.05$ *versus* controls.

more likely to be former or current smokers or both, as shown in Table I.

The association between food group intake and risk of each subtype of cancer is shown in 3 ways. Table II compares the central tendencies of intake for each food group by case/control status, while Table III presents adjusted OR associated with each food group and their component subgroups. Results from modeling each food group and subgroup as a continuous variable are shown, based on increasing intake of 1 serving per day. Table IV presents adjusted OR for each of the major food groups, mutually adjusted for all other primary food groups in the model, with food intakes modeled as a continuous variable based on increasing intake of 1 serving per day. Table V shows the results of stepwise selection models of the various food subgroups.

Esophageal adenocarcinoma

Compared to controls, study subjects with esophageal adenocarcinoma tended to report lower consumption of fruits, vegetables and whole grains and higher consumption of meats, refined grains and high-fat dairy products (Table II). As shown in Table III, based on results from the adjusted logistic regression models, significant inverse associations were found with fruit (OR = 0.85, 95% CI: 0.75, 0.96) and vegetable intake (OR 0.85, 95% CI: 0.75, 0.96), whereas significant positive associations were found for meat intake (OR = 1.43, 95% CI: 1.11, 1.83). After mutual adjustment for all other primary food groups in the model, the inverse association with vegetables and positive association with meat remained statistically significant (Table IV).

Adjusted logistic regression models for each of the food subgroups revealed that noncitrus fruits and deep yellow, dark green

TABLE III – INTAKE OF FOOD GROUPS, AND COMPONENT SUBGROUPS, AND RISK OF ESOPHAGEAL AND GASTRIC CANCER, FROM UNITED STATES MULTICENTER, POPULATION-BASED STUDY

	Esophageal adenocarcinoma		Gastric cardia adenocarcinoma		Esophageal squamous cell carcinoma		Noncardia gastric cancer	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Fruit	0.85	0.75, 0.96	0.95	0.86, 1.06	0.88	0.76, 1.03	0.99	0.90, 1.09
Citrus	0.94	0.73, 1.22	0.87	0.68, 1.12	0.84	0.59, 1.19	1.07	0.86, 1.33
Noncitrus	0.73	0.59, 0.90	0.84	0.68, 1.03	0.72	0.55, 0.93	0.99	0.83, 1.18
Juice	0.77	0.57, 1.03	1.05	0.89, 1.24	1.04	0.83, 1.30	0.94	0.77, 1.15
Vegetables	0.85	0.75, 0.96	0.96	0.85, 1.08	0.86	0.73, 1.01	0.98	0.88, 1.09
Cruciferous	0.56	0.31, 1.03	0.82	0.47, 1.45	0.97	0.44, 2.10	0.91	0.55, 1.48
Deep yellow	0.58	0.35, 0.96	0.92	0.58, 1.46	0.67	0.36, 1.25	1.13	0.78, 1.64
Dark green	0.52	0.32, 0.86	0.83	0.52, 1.32	0.67	0.36, 1.27	0.96	0.64, 1.44
Starchy	1.56	0.93, 2.62	1.12	0.68, 1.86	0.87	0.45, 1.69	0.79	0.48, 1.29
Raw	0.75	0.61, 0.93	0.93	0.78, 1.14	0.75	0.57, 0.99	1.00	0.84, 1.18
Tomato	0.64	0.38, 1.07	0.78	0.48, 1.27	0.74	0.40, 1.42	0.93	0.60, 1.44
Legumes	0.61	0.18, 2.12	1.57	0.50, 4.88	1.03	0.24, 4.47	0.95	0.33, 2.70
Total fruit and vegetable	0.88	0.82, 0.95	0.97	0.90, 1.03	0.90	0.82, 0.99	0.99	0.93, 1.05
Meat	1.43	1.11, 1.83	1.37	1.08, 1.73	1.16	0.87, 1.56	1.39	1.12, 1.71
Fish	1.39	0.61, 3.19	1.79	0.85, 3.80	1.25	0.41, 3.79	1.78	0.88, 3.57
Poultry	1.65	0.97, 2.82	1.89	1.15, 3.11	1.20	0.63, 2.27	1.90	1.19, 3.03
High nitrite	1.34	0.84, 2.15	1.19	0.74, 1.91	1.62	0.91, 2.90	1.88	1.24, 2.84
Red meats	2.49	1.39, 4.46	1.39	0.80, 2.42	2.10	0.99, 4.45	1.37	0.83, 2.25
Alternates	0.86	0.49, 1.52	1.10	0.64, 1.91	0.41	0.19, 0.90	0.63	0.37, 1.07
Grains	1.05	0.89, 1.23	1.20	1.02, 1.42	0.96	0.76, 1.20	1.36	1.17, 1.59
Whole	0.82	0.63, 1.08	1.06	0.83, 1.36	0.82	0.58, 1.16	0.94	0.75, 1.19
Refined	1.16	0.94, 1.44	1.18	0.95, 1.47	1.21	0.92, 1.59	1.51	1.25, 1.82
Dairy	1.16	0.98, 1.39	1.12	0.93, 1.34	1.39	1.11, 1.75	1.00	0.85, 1.19
Low-fat	0.81	0.60, 1.11	0.83	0.59, 1.17	1.03	0.66, 1.59	0.60	0.41, 0.88
High fat	1.34	1.09, 1.63	1.23	1.01, 1.51	1.48	1.16, 1.89	1.18	0.98, 1.41

Results are adjusted OR [adjusted for sex, site (CT, WA, NJ), age, race (white *vs*. other), proxy status, income, education, usual body mass index, cigarettes/day, consumption of beer, wine and liquor each and energy intake] and 95% CI and show association based on increasing intake of 1 serving/day.

TABLE IV – INTAKE OF FOOD GROUPS, WITH ADJUSTMENT FOR ALL OTHER PRIMARY FOOD GROUPS, AND RISK OF ESOPHAGEAL AND GASTRIC CANCER, FROM UNITED STATES MULTICENTER, POPULATION-BASED STUDY

	Esophageal adenocarcinoma		Gastric cardia adenocarcinoma		Esophageal squamous cell carcinoma		Noncardia gastric cancer	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Fruit	0.92	0.81, 1.05	1.00	0.89, 1.13	0.94	0.80, 1.11	1.04	0.94, 1.16
Vegetable	0.86	0.75, 0.99	0.95	0.84, 1.09	0.89	0.75, 1.07	0.94	0.84, 1.06
Meat	1.51	1.16, 1.96	1.51	1.17, 1.95	1.30	0.95, 1.78	1.60	1.27, 2.10
Grain	1.11	0.93, 1.32	1.29	1.08, 1.53	1.03	0.82, 1.31	1.46	1.25, 1.72
Dairy	1.17	0.97, 1.40	1.19	0.98, 1.45	1.40	1.11, 1.77	1.10	0.93, 1.32

Results are adjusted OR [adjusted for sex, site (CT, WA, NJ), age, race (white *vs*. other), proxy status, income, education, usual body mass index, cigarettes/day, consumption of beer, wine and liquor each and energy intake, with mutual adjustment for all other primary food groups] and 95% CI and show association based on increasing intake of 1 serving/day.

TABLE V – LOW AND HIGH ODDS RATIO ESTIMATES FROM MANUAL STEPWISE SELECTION MODELS FOR INTAKE OF COMPONENT SUBGROUPS AND RISK OF ESOPHAGEAL AND GASTRIC CANCER, FROM UNITED STATES MULTICENTER, POPULATION-BASED STUDY

	Food subgroup	Low OR estimate (95% CI)	High OR estimate (95% CI)
Esophageal adenocarcinoma	Red meat	2.75 (1.51, 4.99)	3.02 (1.65, 5.52)
	High-fat dairy	1.31 (1.07, 1.61)	1.36 (1.10, 1.67)
	Raw vegetables	0.76 (0.61, 0.95)	0.79 (0.63, 1.00)
	Refined grains	1.25 (1.00, 1.56)	1.27 (1.02, 1.59)
Gastric cardia adenocarcinoma	Poultry	1.85 (1.12, 3.04)	1.92 (1.16, 3.17)
	High-fat dairy	1.21 (0.98, 1.48)	1.23 (1.01, 1.51)
Esophageal squamous cell carcinoma	High-fat dairy	1.43 (1.11, 1.85)	1.54 (1.20, 1.98)
	Meat alternates	0.42 (0.19, 0.91)	0.45 (0.20, 0.99)
Noncardia gastric cancer	Poultry	1.66 (1.01, 2.74)	1.96 (1.22, 3.14)
	Refined grains	1.51 (1.25, 1.83)	1.58 (1.30, 1.91)
	High-nitrite meats	1.56 (1.01, 2.43)	1.58 (1.30, 1.91)
	Low fat dairy	0.63 (0.43, 0.93)	0.63 (0.43, 0.94)

Results are adjusted OR and 95% CI and show association based on increasing intake of 1 serving/day.–See methods for details of model selection methods and variables included for selection.–Results summarize the lowest and highest point estimate of effect for each subgroup consistently selected using three model selection approaches.

and raw vegetables were each inversely associated with risk, while red meats and high-fat dairy products were positively associated with risk. Across each of the 3 multivariate selection methods, daily intake of raw vegetables was consistently associated with a decreased risk, while consumption of red meat, refined grains and high-fat dairy foods was consistently associated with an increased risk of this cancer (Table V). No consistent association with fish or poultry was found.

Gastric cardia adenocarcinoma

Study subjects with gastric cardia adenocarcinoma, on average, reported consuming more servings per day of meat, refined grains, and high-fat dairy than controls (Table II). After adjustment for potential confounders, intake of both meat and grains was significantly associated with increased risk (37 and 20%, respectively). As shown in Table III, OR for all of the meat subgroups were greater than 1.0, but only poultry reached statistical significance (OR = 1.89, 95% CI: 1.15, 3.11). After mutual adjustment for all other primary food groups in the model, both meat (OR = 1.51, 95% CI: 1.17, 1.95) and grain intake (OR = 1.29, 95% CI: 1.08, 1.53) remained significantly associated with risk, as shown in Table IV. While no relationship was found with total fruit intake, a borderline inverse association was seen with noncitrus fruit (OR = 0.84, 95% CI: 0.68, 1.03). Intake of high-fat dairy products was significantly associated with an increased risk (OR = 1.23, 95% CI: 1.01, 1.51). Based on the model selections used to evaluate the effects of food subgroups, consumption of poultry and high-fat dairy products was consistently associated with an increased risk of this cancer (Table V).

Esophageal squamous cell carcinoma

Study subjects with esophageal squamous cell carcinoma tended to report consuming fewer fruits and vegetables, and more meat, as well as fewer overall calories, than did controls (Tables I and II). These cases also tended to be leaner, were more likely to be current smokers, consumed more beer and liquor and were more likely to be nonwhite as compared to other cancer subtypes and controls. Adjustment for potential confounders revealed a significantly decreased risk associated with total fruit and vegetable intake combined (OR = 0.90, 95% CI: 0.82, 0.99) and a significantly increased risk associated with intake of dairy products (OR = 1.39, 95% CI: 1.11, 1.75; Table III). After mutual adjustment for all other primary food groups in the model, only intake of dairy products remained significantly associated with risk of this cancer (Table IV).

Initial analyses of food subgroups revealed inverse relationships with noncitrus fruits (OR = 0.72, 95% CI: 0.55, 0.93), raw vegetables (OR = 0.75, 95% CI: 0.57, 0.99) and meat alternates (OR = 0.41, 95% CI: 0.19, 0.90), while a positive association was found with high-fat dairy products (OR = 1.48, 95% CI: 1.16, 1.89) and red meats (borderline significant; OR = 2.10, 95% CI: 0.99, 4.45). When we controlled for other food subgroups in the model, using each of 3 selection methods, meat alternates were associated consistently with a decreased risk of this cancer, while high-fat dairy intake was consistently associated with an increased risk (Table V).

Noncardia gastric adenocarcinoma

Study subjects with noncardia gastric adenocarcinoma tended to report consuming more servings per day of meat, mainly poultry and high-nitrite meats, as well as grains, particularly refined grains (Table II). They also reported fewer servings per day of meat alternates and low-fat dairy than controls.

Intake of meats and grains were significantly associated with an increased risk of noncardia gastric adenocarcinomas, after adjusting for potential confounders (OR = 1.39, 95% CI: 1.12, 1.71 and OR = 1.36, 95% CI: 1.17, 1.59, respectively; Table III). Mutual adjustment for all other primary food groups in the model yielded an increase in these OR, as shown in Table IV. Analyses of food subgroups showed significantly increased risks with poultry (OR = 1.90, 95% CI: 1.19, 3.03), high-nitrite meats (OR = 1.88, 95% CI: 1.24, 2.84) and refined grains (OR = 1.51, 95% CI: 1.25, 1.82), and a significantly decreased risk with low-fat dairy products (OR = 0.60, 95% CI: 0.41, 0.88), as shown in Table III. Using each of the 3 stepwise selection methods, strong inverse associations were consistently found with consumption of low-fat dairy products, while positive associations were seen with poultry, high-nitrite meats and refined grains (Table V).

Discussion

In this large population-based case–control study of men and women in the United States, a consistent positive association was found between meat intake and risk of esophageal adenocarcinoma as well as cardia and noncardia gastric adenocarcinomas, whereas an inverse association was seen between combined fruit and vegetable intake and risk of esophageal adenocarcinoma and squamous cell carcinoma. While total vegetable intake was inversely associated with both subtypes of esophageal cancer, statistical significance was reached only for esophageal adenocarcinoma. In addition, grain intake was significantly associated with increased risks of both subtypes of gastric cancer, with the relation to noncardia gastric adenocarcinoma largely driven by intake of refined grains. Furthermore, consumption of high-fat dairy products was associated with an increased risk of both subtypes of esophageal cancer and with gastric cardia adenocarcinoma, and low-fat dairy intake with a decreased risk of noncardia gastric adenocarcinoma.

The World Cancer Research Fund, in a comprehensive review of the literature, concluded that fruit and vegetable intake is protective against esophageal cancer risk, with 18 out of 22 case–control studies reporting significant inverse associations with at least 1 vegetable and/or fruit category.[13] It has been theorized that fruits and vegetables, which are high in antioxidants, phytosterols and other substances, may inhibit carcinogenesis by free-radical quenching or by blocking the formation of N-nitroso compounds.[23–25] Numerous case–control studies have reported that consumption of fruits,[16,26] particularly citrus fruits,[27–32] as well as vegetables,[16,28,29,31–36] lowers the risk of cancers arising in the esophagus and elsewhere in the upper aerodigestive tract. Although the literature on esophageal adenocarcinomas is sparse, Terry *et al*.[16] observed an inverse association between both fruit and vegetable consumption and risk for esophageal adenocarcinoma. Anderson *et al*.[26] also observed an inverse association between fruit intake and risk for esophageal cancer, but observed no association with vegetable consumption. In addition, Cheng *et al*.[37] reported in a study of British women that the risk of esophageal adenocarcinoma was lowest among those in the highest quartile of intake of fruits and “salad vegetables.” Similarly, Zhang *et al*.[38] found a decreased risk for adenocarcinomas of the esophagus and gastric cardia combined among those with higher intakes of noncitrus and raw fruits in a hospital-based case–control study of men and women in the United States (95 incident cases). These findings are consistent with the inverse association we found between intake of noncitrus fruits and dark green, deep yellow and raw vegetables and risk of esophageal adenocarcinoma. In addition, we found that each vegetable subgroup was inversely associated with risk, except for starchy vegetables.

Inverse associations between dietary fiber and esophageal adenocarcinoma have been reported in 2 population-based case–control studies, including the earlier analysis of nutrients in our study.[8,15] Although the present analysis revealed inverse associations between whole grain consumption and risk of both subtypes of esophageal cancer, there were positive associations with refined grains for each of the 4 subtypes of cancer in our study, reaching statistical significance for noncardia gastric adenocarcinoma.

Our finding that high-fat dairy products are associated with an increased risk of both subtypes of esophageal cancer stands in contrast to case–control studies of esophageal cancer that each found no association with dairy products,[39,40] or a reduced risk with higher milk consumption.[18,19] On the other hand, De Stefani *et al.*[41] noted a nonsignificantly increased risk of esophageal cancer with higher intake of dairy foods, while Chen *et al.*[17] reported a 2.5-fold increased risk of esophageal adenocarcinoma with a "high milk" dietary pattern. Given that we found no association between calcium intake and risk of either subtype of esophageal or gastric cancer and positive associations between fat intake and both esophageal and gastric cardia adenocarcinoma in our previous analyses of these data,[15] our findings here suggest that it is likely that the fat content, rather than other components of dairy foods, that are important.

The elevated risk of esophageal adenocarcinoma associated with meat intake is consistent with most previous studies of esophageal cancer overall[18,42–46] and adenocarcinoma in particular.[17,47] Our data further suggest that red meat is driving the association between esophageal adenocarcinoma risk and meat intake, with a greater than 2-fold excess risk at the highest intake of red meat, similar to the findings of Ward *et al.*[47] Contrary to our findings, Launoy *et al.*[48] found an inverse association between meat consumption and esophageal squamous cell carcinoma. The authors, however, note that difference in preparation methods may affect cancer risk[48] and therefore may account, in part, for the different findings. Although mechanisms are unclear, meat is a source of heterocyclic amines (HA), although Terry *et al.*[49] found no association between HA intake and risk of adenocarcinomas of the esophagus and gastric cardia. We were unable to examine any potential association between heterocyclic amine intake, as information on meat cooking practices was not collected. The high level in red meat of a potentially immunogenic molecule, *N*-glycosylneuraminic acid, may also play a role.[50]

Gastroesophageal reflux (GERD) is an established risk factor for esophageal adenocarcinoma, and it is therefore possible that study participants with GERD may have altered their diets in response to their symptoms. Our previous analyses found that the association between total fat intake and risk of esophageal adenocarcinoma was stronger among participants without reflux symptoms compared to those with reflux symptoms.[15] We therefore conducted additional analyses stratified by GERD symptoms (any *vs.* none) for each of the food groups and subgroups and esophageal adenocarcinoma risk. In these analyses, red meat consumption remained a statistically significant risk factor for esophageal adenocarcinoma; however, the observed associations were stronger among participants without reflux (OR = 3.27, 95% CI = 1.20–8.89) compared to those with reflux symptoms (OR = 2.25, 95% CI = 1.08–4.74; data not shown). A similar pattern of risk was observed for high-fat dairy consumption, with a stronger association with esophageal adenocarcinoma risk among persons without reflux (OR = 1.42, 95% CI = 1.00–2.00) compared to those with reflux (OR = 1.32, 95% CI = 1.02–1.72; data not shown). The OR estimates for the other food groups and subgroups associated with risk of esophageal adenocarcinoma changed slightly with stratification for reflux, but did not materially alter our conclusions. Given that cases with GERD may have altered their diet to reduce the frequency of reflux symptoms, particularly avoiding high-fat foods, the true associations for red meat and high-fat dairy intake may be greater than that is reported in this study.

It is noteworthy that meat alternates, including beans and nuts, were associated with a significantly decreased risk of esophageal squamous cell carcinoma in our study, in keeping with previous analyses of these data by Mayne *et al.*,[15] who found a significant inverse association with vegetable proteins. De Stefani *et al.*[41] also reported an inverse association between legume intake and risk of cancers of the upper aerodigestive tract, particularly of the esophagus, although they did not distinguish between subtypes of this cancer. The legumes subgroup, however, was not associated with risk of esophageal squamous cell carcinoma in our study. The primary difference between the meat alternates and legumes food subgroups was the inclusion of nuts and nut products (*e.g.*, peanut butter) in the former category.

In our study, meat consumption was a risk factor for both cardia and noncardia gastric cancers. There is some evidence that the relationship with gastric cancers as a whole is mediated by compounds found in meat products such as nitrites and N-nitroso compounds, including *N*-nitrosodimethylamine (NDMA).[13,51–53] In our earlier analyses, Mayne *et al.*[15] reported a significant positive association between noncardia gastric cancer and nitrite intake, consistent with the notion that processed meats (*e.g.*, bacon, sausage and sandwich meats) that are high in nitrites increase gastric cancer risk.[54,55] Our subgroup analyses add to the evidence by linking noncardia gastric cancer to consumption of high-nitrite processed meats.

In earlier analyses, Mayne *et al.*[15] reported an inverse association between consumption of vegetable protein and risk of cardia and noncardia gastric adenocarcinoma, consistent with the nonsignificant inverse association we observed between intake of meat alternates and risk of noncardia gastric adenocarcinoma. In another study of gastric cancer, Kaaks *et al.*[56] reported a significant inverse trend with consumption of vegetable protein, and a nonsignificant positive association with animal protein. However, Palli *et al.*[53] failed to find any relationship between vegetable protein and gastric cancer risk, although a significantly increased risk was seen for animal protein.

In contrast to our findings for esophageal cancer, and to many previous studies of gastric cancer,[13] we did not find a strong association between fruits or vegetables and either subtype of gastric cancer. Our findings are similar, however, to those of Terry *et al.*[16] who likewise found no association between fruit or vegetable consumption and risk of gastric cardia adenocarcinoma. In our study, however, inverse associations with citrus fruit consumption were suggested for gastric cardia adenocarcinoma and esophageal squamous cell carcinoma, which may reflect the protective effects of vitamin C we previously reported for each of the tumor subtypes.[15] In addition, significant inverse associations were found between noncitrus fruits and both subtypes of esophageal cancer.

The positive association between total grain consumption and both subtypes of gastric cancer in our study is consistent with previous studies suggesting an increased risk of gastric cancer with increasing intake of starchy foods, including potatoes, bread, rice and pasta.[13]

Can the rising incidence of esophageal and gastric cardia adenocarcinomas be explained at least partially by changes in the dietary patterns associated with these cancers? Food consumption trends between 1970 and 1997 indicate that intake of grain products, especially refined grains, has increased,[57] which is interesting in view of the positive association with esophageal adenocarcinoma. However, refined grain intake was also positively associated, in our study, with risk of noncardia gastric adenocarcinoma, which has declined in incidence. While the percentage of adults consuming whole milk has decreased since 1970, intake of cheeses has doubled,[57] which is noteworthy in light of the positive association between high-fat dairy products and risk of adenocarcinomas of the esophagus and gastric cardia. Red meat consumption, a risk factor for both subtypes of esophageal cancer, has declined in frequency in the population, although still accounting for 58% of overall meat consumption, while meat alternates (*e.g.*, eggs and peanut butter) accounted for 12% and fish and shellfish for 8%.[57] Consumption of meat, poultry and fish in mixtures, however, has increased.[58] Finally, while certain subgroups of fruits and vegetables were inversely associated with the cancers under study, trends in consumption have shown little change over time.[58] Therefore, while the available data are limited, upward trends in the intake of refined grains and high-fat dairy products may have contributed in part to the increasing incidence of esophageal adenocarcinoma and gastric cardia adenocarcinoma (high-fat dairy products), but appear not to have contributed to the decreasing incidence of esophageal squamous cell carcinoma or noncardia gastric adenocarcinoma.

As with case–control studies generally, the present study has several limitations, including the potential for recall bias. However, the specificity of risks, which included an inverse association between intake of vegetables and esophageal adenocarcinoma but not the other cancers under study, argues against this bias to some extent. In addition, due to the high case-fatality rate of these cancers, direct interview data could not be obtained from ~30% of cases. However, when separate analyses excluded proxy interviews, the OR estimates remained essentially the same. This was also the case when separate analyses were run for men and women. As reflux is a risk factor for esophageal adenocarcinoma, it is possible that study subjects altered their diet in response to reflux symptoms. Stratified analyses by the presence or absence of reflux symptoms indicated that, while OR estimates changed slightly, they did not alter our conclusions, thus limiting the likelihood of bias in our risk estimates. However, longitudinal studies are needed to examine this possibility further. Although measurement error is inherent to dietary assessment methods, our study utilized a validated food frequency questionnaire[22] that was administered by trained interviewers following a defined protocol in efforts to minimize the potential for differential misclassification. In addition, we were unable to adjust for H. Pylori infection, an established risk factor for noncardia gastric cancer, in these analyses, as blood samples were only available for a subgroup of study subjects.

In conclusion, our population-based case–control study indicated that higher intake of meats, particularly red meats, and lower intake of vegetables were associated with a significantly increased risk of esophageal adenocarcinoma, while higher intake of meats, particularly poultry, and high-fat dairy were associated with an increased risk of gastric cardia adenocarcinomas. These findings offer additional strategies for the prevention of these cancers.

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APPENDIX A1 – ASSIGNMENT OF FOOD ITEMS TO FOOD GROUPS AND COMPONENT FOOD SUBGROUPS

Food group	Subcategory	Food frequency items
Fruits	Juices	Orange juice, grapefruit juice or Vitamin C-enriched fruit drinks
	Citrus	Oranges, grapefruit, or tangerines; cantaloupe in season; other melon, watermelon, or honeydew, in season; strawberries, in season
	Noncitrus	Apples or pears; bananas; peaches, nectarines, plums (fresh or canned); apricots, fresh, canned or dried; other dried fruit, such as raisins or prunes; other fruit, such as fruit cocktail, berries, applesauce, pineapple, or grapes, not juice
Vegetables	Cruciferous	Broccoli; cabbage, sauerkraut, or brussels sprouts; cauliflower; beets; coleslaw
	Deep yellow	Carrots, including in mixed dishes; summer squash, zucchini, or okra; winter squash (acorn or butternut); sweet or bell peppers; sweet potatoes or yams; vegetable soups (0.25)
	Dark green leafy	Broccoli; cooked greens, such as spinach, mustard greens, turnip greens or collard greens; plain lettuce or plain spinach salad
	Starchy	French fries or fried potatoes; boiled, baked, or mashed potatoes; peas; corn; cream soups such as chowders or potato soup (0.5)
	Raw	Avocado or guacamole; fresh tomatoes or tomato juice; mixed green salad with vegetables such as tomatoes or carrots; celery; sweet peppers or bell peppers; hot or chili peppers; plain lettuce or plain spinach salad; onions or leeks, including in cooking; string beans or green beans
	Dry beans and peas (legumes)	Beans, such as baked beans, pinto, kidney, lima and lentils; bean soups such as lentil soup, black bean, minestrone or pea soup (0.75)
	Tomato products	Fresh tomatoes or tomato juice; pizza; spaghetti or other pasta with meat sauce; spaghetti c/o meat sauce
Dairy	Low-fat products	Low fat or part-skim cheese, such as lite-line, included in cooking; Cottage cheese, either regular or low fat; low-fat frozen desserts, including frozen yogurt, sherbet, or ice milk
	High-fat products	Regular cheeses or cheese spreads, including in cooking; yogurt, all types, except frozen; ice cream or milkshakes; pudding, custard, flan; milk and beverages made with milk, such as hot chocolate, not including milk on cereal or in coffee/tea; cream soups such as chowders or potato soup (0.5); pizza (1.25); pasta with cream sauce (1.25)

APPENDIX A1 – ASSIGNMENT OF FOOD ITEMS TO FOOD GROUPS AND COMPONENT FOOD SUBGROUPS (CONTINUED)

Food group	Subcategory	Food frequency items
Breads/cereals	Whole grains	Dark breads, including dark sandwich bread, and dark grain bagels, rolls or pita bread; tortillas of any type; cereals, granola, high fiber, whole grain, cold or cooked
	Refined grains	White breads, including white sandwich bread, and light grain bagels, rolls or pita bread; rice, noodles, or other grains as a side dish; crackers, such as saltines or ritz; cereals, fortified, cold or cooked; pancakes or waffles; pizza (2) spaghetti or other pasta with meat sauce; spaghetti c/o meat sauce; pasta with cream sauce; potato, macaroni salad (0.5)
Meats	Fish	Fried fish, fish sandwich, or fried shellfish, such as shrimp or clams; shellfish, not fried, such as shrimp, lobster, crab or oysters; canned tuna, tuna salad, or tuna casserole; other fish that is broiled or baked; smoked fish or lox; salted or dried fish
	Poultry	Fried chicken; roasted, stewed, or broiled chicken or turkey, as a main dish; nonsmoked chicken or turkey as a lunchmeat or on sandwiches
	High-nitrite meats	Smoked turkey lunchmeat; cured, smoked ham lunchmeat; bologna; salami; hot dogs; sausage, not including breakfast sausage; bacon; breakfast sausage
	Red meats	Ground beef, including hamburgers, meatloaf, meatballs, tacos, *etc*.; baked or cooked ham as a main dish; beef, veal, lamb or pork other than ham as a main dish, such as a steak or roast; liver, including chicken liver and other organ meats; corned beef chili with meat and beans (0.5); spaghetti or other pasta with meat sauce (0.75); stew (0.75)
	Meat alternates	Peanut butter, peanuts or other nuts and seeds; beans, such as baked beans, pinto, kidney, lima and lentils

Number in parentheses refer to the number of servings of that food group from that food item.–Food groups were assigned based on USDA guidelines as outlined by *Using The Food Guide Pyramid: A Resource for Nutrition Educators*. Shaw A, Fulton L, Davis C, Hogbin M. US Department of Agriculture. Food, Nutrition, and Consumer Services Center for Nutrition Policy and Promotion.–Serving size allotment for mixed dishes was based on micronutrient content of those foods compared to other food items.