Dietary patterns and adenocarcinoma of the esophagus and distal stomach[1,2]

Honglei Chen, Mary H Ward, Barry I Graubard, Ellen F Heineman, Rodney M Markin, Nancy A Potischman, Robert M Russell, Dennis D Weisenburger, and Katherine L Tucker

ABSTRACT
Background: Dietary pattern analysis is a unique approach to studying relations between diet and disease.
Objective: Our objective was to describe the dietary patterns of an eastern Nebraska population and investigate the associations between those dietary patterns and risks of adenocarcinoma of the esophagus and distal stomach.
Design: We recruited 124 subjects with esophageal adenocarcinoma, 124 subjects with distal stomach adenocarcinoma, and 449 control subjects in a population-based, case-control study.
Results: Six dietary patterns were identified with the use of cluster analysis. The first dietary pattern represented healthy food choices and had higher energy contributions from fruit and vegetables and grain products and lower energy contributions from red meats, processed meats, and gravy than did the other dietary patterns. In contrast, a second dietary pattern was high in meats and low in fruit and cereals. The other 4 dietary patterns were each characterized by a concentrated energy source: salty snacks, desserts, milk, and white bread, respectively. The test of overall difference in cancer risk across dietary patterns was significant for distal stomach adenocarcinoma ($P = 0.04$) but not for esophageal adenocarcinoma. Risk of esophageal adenocarcinoma was inversely associated with intakes of dairy products, fish, all vegetables, citrus fruit and juices, and dark bread and was positively associated with gravy intake. Risk of distal stomach adenocarcinoma was positively associated with red meat intake.
Conclusions: Our study suggests that a diet high in fruit and vegetables may decrease the risk of esophageal adenocarcinoma and that a diet high in meats may increase the risk of distal stomach adenocarcinoma. *Am J Clin Nutr* 2002;75:137–44.

KEY WORDS Esophagus, stomach, neoplasm, dietary pattern, cluster analysis, cancer

INTRODUCTION

Epidemiologic studies of diet and disease have usually focused on individual foods, food groups, or nutrients. The results of recent large-scale cancer prevention trials of nutrient supplementation generally did not confirm the nutrient associations from observational studies (1–8). Because of the complexity of diets and the potential for interactions between food components, approaches that focus on individual nutrients may miss the true role of diet in cancer etiology.

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Dietary patterns have also been used to describe associations between diet and disease (9–19). Unlike analyses focusing on individual nutrients or foods, pattern analysis captures the variations in overall food intake in a specific population. This approach is useful because people who differ in their intake of one important nutrient or food tend to have different intakes of other important nutrients or foods, which often makes it difficult to attribute any observed associations to an individual food or nutrient. Moreover, by characterizing a healthy diet in an actual population, this approach allows for the dissemination of dietary recommendations in a more practical way.

Dietary patterns were defined in various ways in previous studies, including multivariate methods such as cluster analysis and factor analysis. Subjects with different dietary patterns differ in socioeconomic status, health behaviors, total or disease-specific mortalities, and risks of diseases (9–11, 15–24). Using factor analysis, Slattery et al (18) found that a Western diet high in processed meats, red meat, refined grain, and added sugar was associated with a higher risk of colon cancer, whereas a prudent diet high in fresh fruit, legumes, and vegetables was associated with lower risk. In another case-control study, a significant inverse association between the risk of gastric cancer and several food diversity scores was observed (16).

The incidence of esophageal adenocarcinoma is increasing at one of the fastest rates of any cancer in the United States, and the survival rates are poor (25). The association between dietary factors and risk of this cancer is not well understood. A few studies suggest that greater intakes of nutrients from plant sources, particularly from fruit and vegetables, may be associated with a lower risk and that greater intakes of dietary fat may be associated with a higher risk (26–32). Unlike those for esophageal adenocarcinoma, the incidence of and mortality rates for stomach

[1] From the Human Nutrition Research Center on Aging, Tufts University, Boston; the National Cancer Institute, Divisions of Cancer Epidemiology and Genetics and of Cancer Control and Population Sciences, Bethesda, MD; and the University of Nebraska Medical Center, Department of Pathology and Microbiology, Omaha.

[2] Address reprint requests to MH Ward, Occupational Epidemiology Branch, National Cancer Institute, 6120 Executive Boulevard, EPS-8104, MSC-7420, Bethesda, MD 20892-7420. E-mail: wardm@exchange.nih.gov.

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cancer have been decreasing for decades, and there is no clear explanation for the decrease (33). Studies suggest that diet plays an important role in the prevention of this cancer (34). To increase understanding of the role of dietary factors in the etiology of these cancers, we evaluated the associations between dietary patterns and cancer risks in a population-based, case-control study in eastern Nebraska.

SUBJECTS AND METHODS

Study population

The study was conducted in the 66 counties of eastern Nebraska to investigate associations between agricultural and dietary exposures and esophageal adenocarcinoma, stomach adenocarcinoma, and adult glioma. A detailed description of the methods was published previously (29). Briefly, histologically confirmed incident cases of esophageal and stomach adenocarcinoma were identified from the Nebraska Cancer Registry or 14 participating hospitals covering >90% of the study population between 1 July 1988 and 30 June 1993. All participants were white male or female residents of these 66 counties and were aged ≥21 y. The cases were limited to whites because the controls selected from an earlier study did not include other ethnic groups. The controls were randomly selected from the control group of a previous population-based, case-control study conducted in 1986–1987 in the same base population (35) and were frequency-matched to the overall distribution of all the cancer cases (including adult glioma patients) by age, sex, and vital status. Of those eligible, 137 esophageal adenocarcinoma cases, 170 stomach adenocarcinoma cases, and 502 controls completed interviews; overall response rates were 88%, 79%, and 83%, respectively. After the response rate of the controls in the previous study (87%) was taken into account, the adjusted response rate of the reinterviewed controls in the present study was 72%. The study protocol was approved by the Institutional Review Boards of the National Institutes of Health and the University of Nebraska Medical Center. After obtaining physician consent (for the cases), we sent a letter to the cases and controls that explained the study and invited participation. In a subsequent telephone call, we obtained informed consent from the cases, controls, or their next of kin (for deceased cases and controls) who were willing to participate in the telephone interview.

Interview and dietary assessment

Trained interviewers conducted telephone interviews of the cases and controls or their proxies during 1992–1994. Because of the poor prognoses of these cancers, interviews were conducted with the next of kin for 76% of esophageal adenocarcinoma cases, 80% of stomach adenocarcinoma cases, and 61% of controls. For the controls, self-respondents were intentionally oversampled to increase the power of subgroup analyses among self-respondents.

A modified version of the short Health Habits and History Questionnaire (36) was used for dietary assessment. In previous studies (36, 37), the short questionnaire was validated against the full questionnaire. Some food items, including several high-nitrate vegetables, onions, several processed meats, and fish, were added to the questionnaire. Subjects were asked to recall their frequency of consumption of 54 dietary items before 1985. Cases and controls with unknown intakes for ≥20% of the food items were excluded from the analyses (29). This left 124 (91%) esophageal adenocarcinoma cases, 154 (91%) stomach adenocarcinoma cases, and 449 (89%) controls. Of the stomach adenocarcinoma cases, 124 arose in the distal part of the stomach (hereafter called distal stomach cancer) and 30 in the stomach cardia. According to the Lauren classification (38), 47 of the 124 distal stomach cancer cases were of the diffuse type, 61 were of the intestinal type, 11 were of the mixed type, and 5 either were of other types or were not classifiable. Because of the small number of cardia cases and because cardia cancer is hypothesized to have different risk factors from distal stomach cancer, we excluded cardia cases from our analyses.

Statistical analysis

Before analysis of the data, the 54 food items were sorted into 24 different food groups. Definitions of food groups are shown in **Appendix A**. Beyond major food groups as defined in the food guide pyramid, subgroups were defined on the basis of their similarity or difference in nutrient content. For example, meats from different animal sources differ in their specific fatty acid amounts and composition and therefore were grouped accordingly. The percentage of energy contributed from each food group was calculated and used in the cluster analysis. Standardization by energy contribution helps to remove dietary variations due to differences in sex, age, body size, and physical activity and to retain the proportionally based food-intake patterns.

All statistical analyses were performed with SAS software (version 6.12; SAS Institute, Inc, Cary, NC). We generated dietary patterns among eligible controls by using the cluster analysis procedure PROC FASTCLUS. This procedure classifies subjects into a predetermined number of mutually exclusive groups by comparing Euclidean distances between each subject and each cluster seed in an iterative process. Because cluster analysis is sensitive to outliers, we removed them in 2 ways before making clusters. First, we removed those controls whose energy contribution from any food group was ≥5 times the SD from the mean. Second, because cluster analysis itself is a useful way to identify outliers, we ran the analyses with a predefined number of 20 clusters and removed those clusters with <5 subjects. Through both procedures, a total of 42 (9.4%) controls were identified as outliers and removed, leaving 407 eligible controls for the cluster generation.

To find the most reasonable number of clusters, we ran a series of cluster analyses with predefined cluster numbers from 3 to 10 (22). We compared the ratios of between-cluster variance to within-cluster variance between all runs and constructed Scree plots to examine the ability of these clusters to segregate the study population. Then we scrutinized the food-intake patterns of each set of clusters to see which set provided the clearest separation that was nutritionally meaningful. Finally, we considered statistical power so that we would have reasonable sample sizes for further regression analysis. Once the cluster set was selected, we characterized these dietary patterns by examining their average energy contribution from each individual food group. Cases and outlier controls were finally classified into the nearest cluster by calculating the Euclidean distances between individual subjects and the presaved seed of each cluster.

In univariate analyses, we used one-factor analysis of variance or Student's *t* test to compare means and Mantel-Haenszel chi-square statistics to compare proportions, and multiple comparisons were adjusted with the Bonferroni method. Odds ratios (OR) and 95% CIs were calculated by unconditional logistic regression to estimate associations between individual dietary

TABLE 1
Characteristics of the study population

	Controls (n = 449)	Esophageal adeno-carcinoma (n = 124)	Distal stomach cancer (n = 124)
Age (y)	59.8 ± 17.6[1]	62.3 ± 12.4	70.3 ± 11.4[2]
Male (%)	57.5	87.9[3]	54.0
Self-respondent (%)	42.8	25.0[3]	18.6[3]
BMI (kg/m^2)	25.0 ± 4.4	26.4 ± 3.6[2]	25.3 ± 3.7
Energy intake (MJ)	8.6 ± 3.7	9.2 ± 3.8	9.0 ± 3.7
Alcohol use (%)			
Never drinker	37.9	23.6	47.1[3]
Past drinker	27.2	54.6	37.8
Current drinker	34.9	21.8	15.1
Tobacco use (%)			
Nonsmoker	45.2	21.4[3]	58.4
<30/d	37.6	48.7	28.3
≥30/d	17.2	29.9	13.3
College education (%)	19.0	13.8	6.5[3]
Family history (%)			
Esophageal cancer	0.7	2.5	—
Stomach cancer	5.8	—	20.0[3]
Other gastrointestinal cancer	5.3	13.6[4]	8.7
Ever took vitamin supplement (%)	38.6	28.8	24.8

[1] $\bar{x}$ ± SD.
[2] Significantly different from controls, $P < 0.01$ (Student's t test with Bonferroni adjustment).
[3] Significantly different from controls, $P < 0.01$ (Mantel-Haenszel chi-square test with Bonferroni adjustment).
[4] Significantly different from controls, $P < 0.05$ (Mantel-Haenszel chi-square test with Bonferroni adjustment).

patterns or food groups and risks of the specific cancers. In the dietary pattern analyses, the healthy diet group was used as the reference, and individual 95% CIs and P values were Bonferroni-adjusted with the use of 99% CIs and P values that were multiplied by a factor of 5 to account for the 5 comparisons between each dietary pattern and the reference pattern. The P values for overall differences in cancer risks across dietary patterns were calculated by comparing the −2 log likelihood differences between models with and without the dietary pattern variables and a chi-square distribution with 5 degrees of freedom. All significance tests were two-sided (α = 0.05). In food-group analyses, we tested for a linear trend by including the median of each quartile as a continuous variable in the model and testing for the significance of the slope. We adjusted for age, sex, proxy status, energy intake, body mass index (BMI; in kg/m^2), alcohol use, tobacco use, education, and vitamin supplement use for both cancer sites and age squared for esophageal adenocarcinoma. Family histories of esophageal cancer or gastrointestinal cancer were separately adjusted for esophageal adenocarcinoma and distal stomach cancer because they were associated with the risk in univariate analysis.

RESULTS

Characteristics of the study population are shown in **Table 1**. Esophageal adenocarcinoma cases were more likely to be males and smokers and to have a higher average BMI than were the controls. In a separate analysis, BMI was linearly and positively associated with a risk of esophageal adenocarcinoma after adjustment for potential confounders (OR: 1.1 for each unit increase in BMI; 95% CI: 1.04, 1.18). Stomach cancer cases tended to be older and included lower proportions of drinkers and 4-y college graduates than did the controls. Both groups of cancer cases tended to include higher proportions of subjects with a family history of their respective cancers or other gastrointestinal cancers than did the controls.

The average energy contributions from selected food groups for all 6 clusters among eligible controls are shown in **Table 2**. Compared with the other dietary patterns, the first pattern was characterized by its higher energy contributions from fish, poultry, fruit and vegetables, dark bread, and cereals and lower energy contributions from red meat, processed meat, and gravy. This pattern also had the lowest average energy intake and was the largest group in this population. We termed this pattern a

TABLE 2
Energy contributions from selected foods or food groups for the 6 dietary patterns identified among eligible controls[1]

	Energy contribution					
Food or food group	Healthy (n = 87)	High meat (n = 43)	High salty snacks (n = 72)	High dessert (n = 69)	High milk (n = 56)	High white bread (n = 80)
	%					
Red meat	9.6 ± 3.7	15.7 ± 6.2	11.2 ± 4.5	12.6 ± 4.3	10.5 ± 4.7	9.9 ± 4.1
Processed meat	5.3 ± 3.6	12.1 ± 4.8	6.5 ± 3.2	7.1 ± 3.5	5.4 ± 3.2	6.6 ± 3.7
Fish	1.5 ± 1.3	1.1 ± 1.3	1.3 ± 1.4	1.0 ± 0.8	1.2 ± 1.3	1.2 ± 1.4
Poultry	2.4 ± 1.9	2.0 ± 1.2	2.2 ± 1.9	2.1 ± 1.5	2.0 ± 1.5	1.6 ± 1.5
Gravy	1.2 ± 1.3	1.6 ± 1.2	1.3 ± 1.4	2.0 ± 1.6	1.2 ± 1.3	1.9 ± 1.8
Salty snacks	3.3 ± 3.3	2.3 ± 2.8	8.1 ± 5.5	2.3 ± 2.4	2.3 ± 3.0	2.9 ± 3.8
Milk	15.0 ± 3.2	10.8 ± 4.2	5.7 ± 4.0	6.9 ± 3.8	27.5 ± 5.7	9.1 ± 5.8
Fruit	4.4 ± 2.9	2.2 ± 1.8	3.4 ± 3.2	4.0 ± 2.9	3.4 ± 3.2	3.2 ± 3.2
Vegetables	2.1 ± 1.3	1.8 ± 1.2	1.6 ± 1.1	1.8 ± 1.0	1.8 ± 1.2	1.7 ± 0.9
White bread	4.8 ± 4.1	7.1 ± 3.7	3.4 ± 3.2	5.6 ± 4.0	6.0 ± 4.7	16.9 ± 4.1
Dark bread	4.7 ± 4.2	1.9 ± 2.7	3.8 ± 3.9	3.5 ± 3.9	2.7 ± 3.0	1.6 ± 3.1
Desserts	5.4 ± 3.9	4.3 ± 3.3	4.4 ± 3.0	14.0 ± 5.4	3.9 ± 4.1	5.7 ± 4.2
Cereal	5.6 ± 3.7	2.5 ± 2.3	2.8 ± 2.7	3.4 ± 3.0	4.5 ± 2.9	3.4 ± 3.4
Beans	1.8 ± 1.7	1.9 ± 2.0	1.8 ± 1.7	1.3 ± 1.6	1.5 ± 1.3	1.3 ± 1.3
Total energy intake (MJ)	7.3 ± 2.5	9.9 ± 4.0	9.2 ± 4.2	8.3 ± 3.7	8.7 ± 3.8	8.7 ± 3.0

[1] $\bar{x}$ ± SD; n = 407 after exclusion of outliers.

TABLE 3

Comparison of sample characteristics for the 6 dietary patterns among eligible controls[1]

	Healthy (*n* = 87)	High meat (*n* = 43)	High salty snacks (*n* = 72)	High dessert (*n* = 69)	High milk (*n* = 56)	High white bread (*n* = 80)	*P*[2]
Age (y)	57.5 ± 17.8[a,b,3]	56.6 ± 20.2[a,b]	51.3 ± 17.1[a]	64.4 ± 14.9[b,c]	56.5 ± 18.6[a,b]	66.8 ± 13.5[c]	0.0001
Male (%)	51.7[a,b]	67.4[a,b]	61.1[a,b]	40.6[a]	58.9[a,b]	68.8[b]	0.008
BMI (kg/m^2)	24.7 ± 3.8	26.2 ± 5.9	24.8 ± 3.9	25.2 ± 4.7	24.1 ± 3.2	25.3 ± 3.0	NS
Alcohol use (%)							0.002
Never drinker	42.5[a]	32.6[a,b]	18.0[b]	46.4[a]	39.3[a,b]	40.2[a]	
Past drinker	20.7	27.9	27.8	26.1	28.6	32.5	
Current drinker	36.8	39.5	54.2	27.5	32.1	27.3	
Tobacco use (%)							0.03
Nonsmoker	56.8[a]	50.0[a,b]	34.4[b]	44.8[a,b]	39.2[a,b]	42.6[a,b]	
<30/d	35.8	31.6	37.5	32.8	47.1	41.2	
≥30/d	7.4	18.4	28.1	22.4	13.7	16.2	
College education (%)	24.7	15.0	23.5	10.8	25.0	14.1	NS
Family history (%)							
Any cancers	41.8	42.5	55.9	54.1	47.2	52.8	NS
Gastrointestinal cancers	8.9	7.5	13.2	11.5	9.4	13.9	NS
Ever took vitamin supplement (%)	53.4[a]	20.9[b,c]	41.2[a,b]	35.4[a,b]	50.0[a,b]	23.0[c]	0.001

[1] *n* = 407. Values in the same row with different superscript letters are significantly different, $P < 0.05$ (after Bonferroni adjustment).

[2] One-factor ANOVA was used for comparison of means, and the chi-square statistic was used for comparison of proportions. *P* values are across all of the dietary patterns.

[3] $\bar{x}$ ± SD.

healthy diet. In contrast with this pattern, the second dietary pattern (termed a high-meat diet) had the highest energy intake among all 6 patterns and was the highest in red meat, processed meat, and beans and the lowest in fruit, cereals, and salty snacks. The third dietary pattern was distinguished from the others by its relatively higher energy contribution from salty snacks and was termed a high-salty-snacks diet. In comparison with the other patterns, this pattern had the lowest energy contributions from milk, vegetables, and white bread and a low energy contribution from cereals. The fourth dietary pattern (termed a high-dessert diet) had a substantially higher energy contribution from desserts and a higher contribution from gravy than did the other groups but relatively lower energy intakes from fish, salty snacks, and beans. It also had a relatively high energy contribution from fruit, similar to the healthy diet. The fifth dietary pattern (termed a high-milk diet) had a 2–5-fold higher energy contribution from milk than did the other groups and relatively lower contributions from gravy, salty snacks, and desserts. The last dietary pattern was characterized by a relatively high energy contribution from white bread and a relatively low energy contribution from dark bread and was thus termed a high–white bread diet. This pattern also had the lowest energy contribution from poultry and beans.

The population distributions of age, sex, alcohol use, cigarette use, and vitamin supplement use differed between the dietary patterns (**Table 3**). Approximately equal numbers of men and women had a healthy diet. Compared with the other dietary groups, the healthy diet group was less likely to smoke cigarettes and more likely to take vitamin supplements; this group also had a low proportion of alcohol drinkers. Approximately two-thirds of the eligible controls in the high-meat diet group were men, and this group included the lowest proportion of vitamin-supplement users and had a low average education level. This group also tended to have the highest average BMI, although it was not significantly different from that of the other groups. The high–salty snacks diet group tended to be younger, had higher proportions of smokers and alcohol drinkers than did the other groups, and had a high average education level. The high-dessert diet group tended to be older and was more likely to include women, whereas the high–white bread diet group was the oldest and had more men than did the other groups. Moreover, both of these groups tended to have a relatively low proportion of college graduates. The high-milk diet group, like the healthy diet group, had a higher proportion of vitamin-supplement users and tended to have a higher proportion of college graduates and a lower BMI.

The ORs for the individual dietary patterns compared with the healthy dietary pattern are presented in **Table 4**. The test for overall difference in cancer risk across dietary patterns was significant ($P = 0.04$) for distal stomach cancer. However, because of small sample sizes, in particular, the small number of cases of esophageal adenocarcinoma with a healthy diet, this test was not significant for esophageal adenocarcinoma. When individually compared with the healthy dietary pattern, the high-meat dietary pattern was associated with a 3.6-fold higher risk of esophageal adenocarcinoma (Bonferroni-adjusted 95% CI: 0.96, 13.2) and a 2.9-fold higher risk of distal stomach cancer (95% CI: 0.89, 9.2). A ≥2-fold higher risk of esophageal adenocarcinoma was also found for the high–salty snacks dietary pattern (OR: 2.9; 95% CI: 0.85, 9.9), the high-milk dietary pattern (OR: 2.5; 95% CI: 0.64, 9.8), and the high–white bread dietary pattern (OR: 2.6; 95% CI: 0.77, 8.7), and a ≥2-fold higher risk of distal stomach cancer was found for the high-milk dietary pattern (OR: 2.2; 95% CI: 0.68, 7.0). However, none of these comparisons were significant after Bonferroni adjustment for multiple comparisons.

ORs and 95% CIs for adenocarcinoma of the esophagus and distal stomach are presented in **Table 5** by quartiles of food or food group intake. For esophageal adenocarcinoma, the highest intake quartiles of dairy products, fish, all vegetables, citrus fruit and juices, and dark bread were each associated with a ≥50% lower risk compared with the lowest intake quartiles, and the inverse trends were significant. We also observed a 40–60% lower risk for the highest intake quartiles of milk, poultry, dark-yellow vegetables, tomatoes, and total cereals compared with the lowest intake quartiles. Gravy intake was positively associated with a risk of esophageal adenocarcinoma. For distal stomach cancer,

TABLE 4
Odds ratios (ORs) and 95% CIs of esophageal adenocarcinoma and distal stomach cancer for each dietary pattern compared with the healthy dietary pattern

	Controls	Esophageal adenocarcinoma			Distal stomach cancer		
Dietary pattern	*n*	*n*	OR[1]	*P*[2]	*n*	OR	*P*[2]
Healthy	104	13	1.0	—	27	1.0	—
High meat	48	26	3.6 (0.96, 13.2)	0.06	21	2.9 (0.89, 9.2)	0.1
High salty snacks	85	28	2.9 (0.85, 9.9)	0.2	13	1.5 (0.45, 5.2)	1
High dessert	69	14	1.6 (0.39, 6.9)	1	15	0.70 (0.21, 2.4)	1
High milk	57	15	2.5 (0.64, 9.8)	0.4	23	2.2 (0.68, 7.0)	0.4
High white bread	86	28	2.6 (0.77, 8.7)	0.2	25	1.1 (0.37, 3.2)	1

[1] Adjusted for age, sex, energy intake, respondent type, BMI, alcohol use, tobacco use, education, family history, vitamin supplement use for both types of cancer, and for age squared for esophageal adenocarcinoma; 95% CIs for individual comparisons with the reference group are given in parentheses.

[2] The *P* values for overall differences in cancer risks across dietary patterns are 0.12 for esophageal adenocarcinoma and 0.04 for distal stomach cancer.

only higher intakes of red meat were significantly associated with greater risk.

DISCUSSION

In the present study, we used cluster analysis to classify an eastern Nebraska population into 6 dietary patterns. The sharpest contrast in dietary composition was found between the healthy dietary pattern and the high-meat dietary pattern. Twenty-one percent of the eligible controls had a healthy dietary pattern that was characterized by the lowest average energy intake and food choices that were relatively consistent with the 2000 *Dietary Guidelines for Americans*, which calls for daily intakes of a variety of fruit, vegetables, and whole grains and low intakes of saturated fat and cholesterol (39). In contrast with this healthy dietary pattern, the high-meat dietary pattern included much higher intakes of meats and much lower intakes of fruit, dark bread, and cereals. Both fruit and vegetables and meats are thought to play important roles in cancer etiology. Our dietary pattern analyses suggest that consumption of fruit and vegetables tends to be inversely associated with meat intake within individual diets. Intake of these foods may interact to increase or decrease cancer risk, and this interaction may make it difficult to tease out associations between individual foods and cancers.

The dietary patterns identified in the present study were associated with other demographic characteristics and health behaviors that may affect cancer risk, and these associations are consistent with those found in other studies (14, 18, 21, 40). Such associations show that dietary patterns are imbedded in larger health behavior patterns. This suggests target populations for nutritional education or intervention and points to the importance of considering dietary behavior in a wider context.

A few studies suggest that risk of esophageal adenocarcinoma is inversely associated with nutrient intake from plant sources

TABLE 5
Odds ratios and 95% CIs by quartile (Q) of food or food group intake[1]

	Esophageal adenocarcinoma (*n* = 124)				Distal stomach cancer (*n* = 124)			
Food or food group	Q2	Q3	Q4	*P* for trend	Q2	Q3	Q4	*P* for trend
		times/wk				*times/wk*		
Dairy products	0.85 (0.41, 1.7)	0.46 (0.21, 1.0)	0.43 (0.18, 0.98)	0.02	0.79 (0.35, 1.7)	1.4 (0.68, 2.8)	0.76 (0.34, 1.7)	NS
Milk	0.84 (0.41, 1.7)	0.65 (0.30, 1.4)	0.59 (0.27, 1.3)	NS	0.72 (0.33, 1.6)	1.7 (0.85, 3.5)	0.86 (0.39, 1.9)	NS
Total meat	1.5 (0.66, 3.5)	1.9 (0.80, 4.3)	1.6 (0.61, 4.1)	NS	0.53 (0.22, 1.3)	1.8 (0.85, 3.9)	0.97 (0.40, 2.3)	NS
Processed meat	1.2 (0.50, 2.7)	0.85 (0.38, 1.9)	1.7 (0.71, 3.9)	NS	1.7 (0.77, 3.7)	1.2 (0.55, 2.7)	1.7 (0.72, 3.9)	NS
Red meat	0.93 (0.49, 2.1)	1.0 (0.46, 2.2)	1.4 (0.61, 3.2)	NS	0.96 (0.41, 2.3)	1.5 (0.64, 3.3)	2.0 (0.85, 4.7)	0.05
Poultry	0.71 (0.38, 1.3)	0.53 (0.25, 1.1)	0.47 (0.17, 1.3)	NS	1.5 (0.76, 2.9)	1.0 (0.48, 2.2)	0.88 (0.35, 2.2)	NS
Fish	0.61 (0.31, 1.2)	0.28 (0.14, 0.57)	0.14 (0.04, 0.48)	0.0001	0.88 (0.44, 1.8)	0.61 (0.32, 1.2)	0.58 (0.25, 1.4)	NS
Gravy	1.1 (0.45, 2.6)	1.3 (0.62, 2.8)	3.8 (1.6, 8.8)	0.0003	1.3 (0.56, 3.1)	1.7 (0.81, 3.5)	2.2 (1.0, 4.9)	NS
All vegetables	0.64 (0.32, 1.3)	0.51 (0.25, 1.0)	0.45 (0.20, 1.0)	0.04	1.7 (0.77, 3.6)	1.6 (0.73, 3.4)	1.7 (0.77, 3.7)	NS
Dark-green vegetables	0.77 (0.38, 1.6)	0.86 (0.40, 1.8)	0.81 (0.37, 1.8)	NS	0.53 (0.26, 1.1)	1.3 (0.66, 2.5)	0.63 (0.29, 1.4)	NS
Dark-yellow vegetables	0.62 (0.31, 1.2)	0.49 (0.24, 1.0)	0.49 (0.23, 1.1)	0.05	0.80 (0.37, 1.7)	1.2 (0.59, 2.4)	1.2 (0.57, 2.5)	NS
Tomatoes	0.97 (0.47, 2.0)	0.79 (0.39, 1.6)	0.50 (0.21, 1.2)	NS	2.0 (0.89, 4.3)	1.8 (0.82, 4.0)	1.8 (0.78, 4.0)	NS
Onions	1.4 (0.62, 3.3)	2.0 (0.86, 4.6)	1.9 (0.85, 4.5)	NS	1.8 (0.81, 4.1)	2.4 (1.1, 5.4)	2.1 (0.90, 4.7)	NS
Other vegetables	0.79 (0.38, 1.7)	0.94 (0.46, 1.9)	0.62 (0.28, 1.4)	NS	1.5 (0.69, 3.1)	1.6 (0.72, 3.3)	1.4 (0.65, 2.8)	NS
Citrus fruit and juices	0.75 (0.37, 1.5)	0.47 (0.22, 0.97)	0.48 (0.21, 1.1)	0.03	1.1 (0.54, 2.2)	0.57 (0.27, 1.2)	0.84 (0.40, 1.7)	NS
White bread	1.2 (0.45, 3.1)	1.8 (0.86, 3.9)	1.5 (0.66, 3.5)	NS	2.4 (0.99, 5.7)	1.3 (0.59, 2.9)	1.2 (0.54, 2.7)	NS
Dark bread	0.81 (0.39, 1.7)	0.35 (0.16, 0.78)	0.25 (0.12, 0.52)	0.0001	1.9 (0.93, 4.1)	0.87 (0.40, 1.9)	0.75 (0.36, 1.5)	NS
Cereals	1.2 (0.62, 2.2)	0.60 (0.27, 1.3)	0.56 (0.24, 1.3)	NS	1.2 (0.62, 2.4)	0.74 (0.35, 1.5)	0.71 (0.32, 1.6)	NS
Desserts	2.0 (0.89, 4.3)	1.3 (0.55, 3.1)	1.1 (0.44, 2.7)	NS	1.4 (0.69, 3.0)	0.58 (0.25, 1.3)	0.79 (0.35, 1.8)	NS
Salty snacks	1.0 (0.45, 2.3)	1.2 (0.56, 2.4)	0.85 (0.38, 1.9)	NS	1.4 (0.69, 2.9)	1.2 (0.58, 2.4)	0.67 (0.28, 1.6)	NS

[1] Compared with the lowest intake quartile after adjustment for age, sex, energy intake, respondent type, BMI, alcohol use, tobacco use, education, family history, and vitamin supplement use for both types of cancer, and for age squared for esophageal adenocarcinoma. 95% CIs in parentheses.

and positively associated with dietary fat intake (26–32). Our analyses of dietary patterns and food groups support these findings. For example, the healthy diet group tended to have the lowest risk of esophageal adenocarcinoma, and the high-meat group had a 3.6 times higher risk than did the healthy diet group. In addition, the high-meat group had an almost 3-fold higher risk for distal stomach cancer.

In our food-group analysis, a lower risk of esophageal adenocarcinoma was associated with greater intakes of foods that were frequently consumed in the healthy dietary pattern, including fruit and vegetables and dark bread. These foods are good sources of carotenoids, vitamin C, dietary fiber, and B vitamins, which have been shown to be inversely associated with a risk of esophageal adenocarcinoma (26–28, 30, 32). The strongest inverse association with a risk of esophageal adenocarcinoma was found for the intake of fish, which was also more commonly consumed by the healthy diet group. Fish is a rich dietary source of $n-3$ fatty acids, including eicosapentaenoic acid and docosahexaenoic acid. These long-chain fatty acids can suppress mutation, inhibit cell growth, and enhance cell apoptosis, possibly by inhibiting eicosanoid production from $n-6$ fatty acids (41–43). The healthy dietary pattern was also characterized by the lowest gravy intake, which had a strong positive association with risk of esophageal adenocarcinoma. In addition to its high fat content, gravy usually contains certain cooking carcinogens such as heterocyclic amines (44). For distal stomach cancer, only the intake of red meat was positively associated with risk, which supports the association we observed between the high-meat dietary pattern and distal stomach cancer. Although many other epidemiologic studies found significant inverse associations between intakes of fruit and vegetables and risk of stomach cancer, we did not.

The present study had several limitations. Although our questionnaire requested detailed information regarding intakes of vegetables and processed meats, it was a short version that included only 54 food items. Because of the poor survival rates for these cancers, a substantial amount of information was obtained from proxy respondents. Selection bias can occur if the dietary exposure distribution among dead controls differs from that of the base population (45). However, in the present study, proxy controls reported intakes similar to those reported by self-respondent controls for most food items after adjustment for age, sex, and energy intake. For example, the adjusted mean intakes of dark-yellow vegetables were 2.56 and 2.42 servings/wk for self-respondents and proxy controls, respectively. For citrus fruit and juices, adjusted mean intakes were 2.47 and 2.49 servings/wk, respectively. Information bias can be introduced if cases report intakes that were affected by symptoms of their cancers or that they believe were related to these cancers. However, we observed different associations with dietary patterns and food intakes for esophageal adenocarcinoma and distal stomach cancer, although both types of cancer may be perceived by the general population as having similar risk factors. Moreover, little was known about diet and esophageal adenocarcinoma at the time of the present study. Although recalled diet was found to be more closely associated with past diet than with current diet (46), recall over many years contains errors due to failures in memory (47). However, to the extent that such errors were random, they would have attenuated the observed associations.

Small sample sizes limited our power to detect statistical differences. Despite the relatively large magnitudes of the ORs in the dietary pattern analyses, none of the individual comparisons were significant after the conservative Bonferroni adjustment for multiple comparisons. Therefore, our results need to be confirmed in larger studies.

Cluster analysis is an empirical technique, and the selection of clusters is largely subjective. However, we performed the analyses with varying numbers of clusters and the results were similar. Moreover, the dietary patterns defined in this analysis were not established a priori but were instead based on the data. Finally, the nutritional implications of the 6 dietary patterns were generally understandable, making them directly useful for dietary guidance.

Cluster analysis is data dependent, and the generalizability of the results of this method is a concern. However, different investigations within various populations generated similar dietary patterns (14, 21, 22, 40, 48, 49), usually including high-meat, healthy, high–white bread, and high-milk dietary patterns.

In summary, we found cluster analysis to be a useful tool for generating dietary patterns to investigate associations between diet and disease. Our results suggest that a diet high in fruit and vegetables and whole grains tends to reduce the risk of esophageal adenocarcinoma and that a diet high in meat tends to increase the risk of distal stomach adenocarcinoma.

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APPENDIX A

Definition of the food groups used in the cluster analysis

Food groups	Items
Milk	2%-fat, 1%-fat, or skim milk or beverages made with milk; whole milk or beverages made with whole milk
Cheeses	Cheeses and cheese spread, not including cottage cheese
Ice creams	Ice creams
Processed meats	Bacon; sausage, including breakfast sausage; processed or smoked ham bought from store; meat that was cured or smoked at home; sandwich meats, such as bologna or salami; hot dogs
Red meats	Beef, such as steak or roasts; beef stew or pot pie; hamburgers, cheeseburgers, or meatloaf; fresh ham, ham roast, pork chops, or pork roast; liver, including chicken liver
Chicken or turkey	Chicken or turkey
Fish	Fish, fresh, frozen, or canned, such as stout or tuna fish
Egg	Egg
Gravy	Gravy made from meat juice
Pasta	Spaghetti, lasagna, or other pasta with tomato sauce
All vegetables	Dark-green vegetables; dark-yellow vegetables; tomatoes or tomato juice; onions; celery; lettuce or green salad; radishes; green beans; cole slaw, cabbage or sauerkraut; beets; rhubarb
Dark-green vegetables	Broccoli; spinach
Dark-yellow vegetables	Carrots or mixed vegetables with carrot; sweet potatoes or yams
Fried potatoes	French fries and fried potatoes
Potatoes	Other potatoes, including baked, potato salad, and mashes
Beans	Beans, dry peas, and chili
Fruits	Citrus fruit and juices; cantaloupe
Citrus fruit and juice	Oranges, tangerines, or grapefruits; orange juice or grapefruit juice
White bread	White bread including sandwiches, bagels, and crackers
Dark bread	Dark bread, including whole wheat, rye, and pumpernickel
Cereals	Highly fortified cereal; cooked cereal; other cold cereal
Desserts	Doughnuts, cookies, cakes, or pastry; pie
Butter or margarine	Butter on bread or rolls; Margarine on bread or rolls
Peanuts or peanut butter	Peanuts or peanut butter
Salty snacks	Salty snacks such as chips or popcorn
All soups	Vegetable soups or minestrone; other kind of soups
All other drinks	Fortified fruit drinks; other soft drinks (not diet)