

Dietary Patterns and Risk of Squamous-Cell Carcinoma and Adenocarcinoma of the Esophagus and Adenocarcinoma of the Gastric Cardia: A Population-Based Case-Control Study in Sweden

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Abstract: We conducted a large population-based case-control study in Sweden to examine the association of dietary patterns and the development of cancers from the esophagus or gastroesophageal junction. In total 185 patients with esophageal adenocarcinoma, 165 with esophageal squamous-cell carcinoma, 258 with gastric cardia adenocarcinoma, and 815 randomly selected population controls underwent face-to-face interviews. Exploratory factor analysis was used to identify possible dietary patterns. Multivariate logistic regression with adjustments for age, sex, years of education, body mass index, physical activity, symptomatic gastroesophageal reflux, smoking, and total energy intake was used to estimate odds ratios (ORs) and their 95% confidence intervals (CIs). We identified three major dietary patterns in this population, for example, “healthy diet” (high in vegetables, tomato, fruits, fish, and poultry), “Western diet” (high in processed meat, red meat, sweets, high-fat dairy, and high-fat gravy), and “alcohol drinker” (high in intakes of beer, liquor, and French fries). We found that a healthy diet tended to moderately decrease the risk of all three cancers under study, although none of the associations was statistically significant. A high score of Western diet was associated with increased risks of gastric cardia adenocarcinoma (high 3rd tertile vs. low 1st quartile, OR = 1.8, 95% CI = 1.1–2.9, P for trend = 0.04) and esophageal adenocarcinoma (high 3rd tertile vs. low 1st tertile, OR = 1.6, 95% CI = 0.9–3.1, P for trend = 0.13), whereas a dietary pattern characterized by high beer and liquor intake (alcohol drinker) significantly increased the risk of squamous-cell carcinoma of the esophagus (3rd tertile vs. low 1st tertile, OR = 3.5, 95% CI = 1.9–6.3, P for trend < 0.0001). Our study confirms the important role of diet in the carcinogenesis of esophageal and cardia cancer.

Introduction

In 1990, incidence of esophageal cancer worldwide ranked number 6 among men and number 9 among women

(1). Esophageal cancer is characterized by wide variation in incidence and mortality in different geographical areas. Since the 1970s, the incidence of esophageal adenocarcinoma, previously rather rare, started to rise in Western populations (2), including Sweden (3). The changing epidemiology of esophageal cancer was particularly marked in men.

In Western society, tobacco and alcohol consumption seem to be the primary risk factors of esophageal squamous-cell carcinoma, whereas the known strong risk factors for esophageal adenocarcinoma include gastroesophageal reflux diseases (4–7) and high body mass index (BMI) (8–12). A number of studies have also tried to explore the role of diet and the risk of both histologic types of esophageal cancer in Western populations, but mainly focused on individual food items (13). However, people who differ in consumption of one important nutrient or individual food item tend to differ in main consumption of other important nutrients or food items. Thus, the attribution of an increased or decreased risk of esophageal cancer to one particular nutrient or food item may sometimes be inappropriate, if strong correlations between items prohibit the full disentanglement. Furthermore, a small effect of a particular nutrient is difficult to be found and also looking for effects of a large number of nutrients or food items increases the probability of chance findings. Focusing on dietary patterns can help find the role of overall diet in cancer etiology, which has been demonstrated in several previous studies (14–16), including one on esophageal cancer (17). Thus, dietary pattern analysis is useful as a complementary approach to more traditional analysis of individual nutrients or food items (18).

To enhance understanding of the role of dietary factors in the etiology of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia, as well as to provide a dietary guideline that has an important public health implication, we tried to identify major dietary patterns in our study population, and we studied their associations with the risk of the three cancer types in a nationwide population-based case-control study in Sweden.

Material and Methods

The study design has been described in full elsewhere (5). Briefly, the study encompassed the whole population of Sweden <80 yr of age. In this study we selected all newly diagnosed patients with adenocarcinoma of the esophagus (216 cases) or gastric cardia (313 cases) and half of the patients with squamous-cell carcinoma of the esophagus (228 cases born on even-numbered days) between 1995 and 1997. A comprehensive organization for the rapid ascertainment of cases ensured that every potential case patient throughout the study area was identified soon after diagnosis. All the cases were classified in the same way for histological and anatomical aspects. The study pathologist reviewed histological slides. Endoscopists, surgeons, and pathologists gave standardized, detailed descriptions of the location of the cancer in the cases. The adenocarcinomas with a center within 2 cm proximal or 3 cm distal to the gastroesophageal junction and without evidence of Barrett's esophagus were classified as a cancer of the gastric cardia. Squamous-cell carcinomas were classified as esophageal even if the location was seemingly in the gastric cardia. If Barrett's esophagus was detected adjacent to cardia adenocarcinoma, the tumors were classified as esophageal. The control subjects were selected randomly from the Swedish population and frequently matched to resemble the age and sex distribution among the esophageal adenocarcinoma cases through the use of the Total Population Register, which is computerized and updated continuously.

In total, 189 (88%) patients with esophageal adenocarcinoma, 167 (73%) of those with esophageal squamous-cell carcinoma, 262 (84%) of those with gastric cardia adenocarcinoma, and 820 (73%) of population controls underwent computer aided face-to-face interviews by specially trained professional interviewers from Statistics Sweden. Main reasons for nonparticipation among cancer patients were poor clinical condition or death shortly after diagnosis, whereas that for controls was unwillingness. We excluded 8

subjects from the analysis because their log scales of total energy intake were <3 or >3 SD from the mean, indicating errors in their responses to the dietary questions. We further excluded 4 subjects due to missing BMI and another 3 subjects due to poor responses regarding dietary questions. Finally 185 cases with esophageal adenocarcinoma, 165 with esophageal squamous-cell carcinoma, 258 with gastric cardia adenocarcinoma, and 815 controls remained for analysis. Their characteristics are shown in Table 1.

Dietary Assessment

A structured food frequency questionnaire, a modified version of a previously evaluated questionnaire including 63 food and beverage items of interest (19), was used to evaluate dietary habits of the controls and cases 20 yr before interview. The usual frequency of consumption of each food item was asked and answers were in terms of number of times per day, week, month, or year. We transformed the data into average monthly intake for every food item, by assuming 1 mo equal to 4 wk or 30 days. To reduce the complexity of data we grouped the individual items into 26 separate food groups as shown in the Appendix. Grouping was based on the similarity of nutrient profiles or their association with cancer and is similar to what has been used in previous Swedish studies (15,16,20).

Besides the dietary history, the questions covered demographic characteristics, living conditions during childhood and adolescence, gastroesophageal reflux symptoms, anthropometric measures, smoking, history of medication use, and occupational history.

Statistical Methods

We used principal components method for factor analysis in SAS (version 8.2; SAS Institute, Cary, NC) to identify potential dietary patterns among population controls only. Using the correlation matrix of the 26 food groups, orthogo-

Table 1. Characteristics of the Subjects in a Case-Control Study of Esophageal and Gastric Cardia Cancer, Sweden

	Esophageal Adenocarcinoma	Esophageal Squamous-Cell Carcinoma	Gastric Cardia Adenocarcinoma	Controls
Number	185	165	258	815
Age (median, yr)	69	67	66	68
Male (%)	162 (88)	118 (72)	219 (85)	675 (83)
Symptomatic gastroesophageal reflux (%)	111 (60)	25 (15)	74 (29)	135 (17)
Body mass index (median, kg/m ²)	25.4	23.6	24.7	23.7
Smoking history (2 yr before interview)				
Never smoker (%)	56 (30)	22 (13)	43 (17)	323 (40)
Missing pack year (%)	13 (7)	6 (4)	14 (5)	43 (5)
Ex-smoker, pack year <15 (%)	36 (20)	15 (9)	53 (21)	160 (20)
Ex-smoker, pack year ≥15 (%)	38 (21)	25 (15)	63 (24)	119 (14)
Current smoker, pack year <30 (%)	23 (12)	41 (25)	39 (15)	97 (12)
Current smoker, pack year ≥30 (%)	19 (10)	56 (34)	46 (18)	73 (9)
Years of education (yr)				
0-6 (%)	47 (25)	40 (24)	43 (17)	180 (22)
7-10 (%)	92 (50)	77 (47)	124 (48)	317 (39)
10+ (%)	46 (25)	48 (29)	91 (35)	318 (39)

nal varimax rotation method was applied to achieve simpler structure facilitating interpretation. Although factors with eigenvalues (a measure of the amount of variance that is accounted for) greater than 1.0 indicate that the factor describes more of the variability in the data than the average variable for any individual item within the factor, selection of factors was based on interpretability and Scree plot (21). In fact, Scree plot showed a clear break, and we selected all three factors with eigenvalues greater than 1.5. Factor loadings are correlation coefficients between food groups and dietary patterns and a positive loading in a factor indicates a direct association with the factor, whereas a negative loading indicates that the food group is inversely associated with the factor. We then calculated for each study subject factor scores for these three dietary patterns. Factor scores were divided into tertiles according to the distribution in controls. We used χ^2 tests to check the differences of distribution of categorical variables (e.g., symptomatic gastroesophageal reflux and smoking), and analysis of variance tests to check differences of distribution of continuous variables (e.g., BMI) across dietary pattern score categories.

Unconditional logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals (CIs). Age, sex, years of education, symptomatic gastroesophageal reflux, BMI, smoking (a combination of smoking status and pack/years), physical activity, and total energy intake were considered as potential confounders and were also included in the models. As a basis for the linear trend tests across categories of dietary pattern scores, each subject was assigned the median value of the specific category, and this variable was treated as continuous variable in modelling. All *P* values reported are two-sided.

Ethical Considerations

This study was approved by all regional ethics committees in Sweden. Individual written informed consent was obtained before the interview.

Results

Table 2 shows correlations between individual foods and the three pattern factors with eigenvalues greater than 1.5. The first dietary pattern, accounting for 9% of the variability, was characterized by high intake of foods generally thought to be healthy including vegetables, tomato, fruits, fish, and poultry, and was thus labelled as “healthy diet,” whereas the second dietary pattern, labelled as “Western diet,” was characterized by high consumption of processed meat, red meat, sweets, high-fat dairy, and high-fat gravy. The third pattern was loaded heavily on alcoholic beverages including beer and liquor and French fries and arbitrarily labelled as “alcohol drinker” to be comparable to previous studies in Sweden. Median consumptions of chosen food groups by tertiles of 3 dietary pattern scores among controls are shown in Table 3.

Table 2. Assessment of Factor-Loading Matrix Among Control Subjects in a Factor Analysis of Dietary Intake Patterns and Risk of Esophageal and Gastric Cardia Cancer, Sweden^a

	Healthy Diet	Western Diet	Alcohol Drinker
Vegetables	0.76	–	–
Tomato	0.61	–0.26	–
Fruits	0.56	–	–0.22
Fish	0.50	0.17	–
Poultry	0.48	–	–
Juice	0.38	–0.21	–
Low-fat dairy	0.29	–0.18	–
Refined grains	0.22	–	–
Nuts	–	–	–
Processed meat	–	0.59	0.24
Red meat	0.23	0.50	0.37
Sweets	0.17	0.49	–0.37
High-fat dairy	–0.21	0.47	–
High-fat gravy	–	0.41	–
High-energy drinks	–	0.34	–
Whole grains	–	0.34	–
Coffee	–	0.33	0.22
Potato	–	0.21	0.16
Wine	–	–0.16	–
Tea	–	–0.37	–
Beer	–	–	0.60
French fries	0.18	0.19	0.54
Liquor	–	–	0.47
Egg	–	0.21	0.36
Dressing sauce	0.18	–	0.35
Cereal	0.20	–	–0.35
Proportion of variability (%)	9	9	6

a: Values of <0.15 were not shown in the table for simplicity.

b: Loadings >0.40.

Table 4 shows distribution of some established risk factors for esophageal and gastric cardia cancer according to tertiles of the three dietary pattern scores among controls. In general, there were no obvious differences of distribution of symptomatic gastroesophageal reflux across any of the three dietary patterns. Subjects who had high factor scores for the healthy diet were less likely to be smokers, whereas those having high Western diet scores, on average, had higher BMI and total energy intake. Subjects having high alcohol drinker scores were more likely to be smokers and had low BMI or total energy intake.

The ORs and their 95% CIs for adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia by tertiles of dietary patterns scores are shown in Table 5. After controlling for the potential confounding effects of age, sex, symptomatic gastroesophageal reflux, years of education, BMI, smoking, physical activity, and total energy intake, the healthy diet pattern was, in general, associated with moderately reduced risks, albeit non-statistically significant, for three cancer types under study. In contrast, the Western diet pattern was associated with an obviously increased risk for gastric cardia adenocarcinoma (highest vs. lowest tertiles, OR = 1.8, 95% CI =

Table 3. Characteristics of Dietary Patterns by Consumption of Chosen Food Groups Among Control Subjects (median servings/mo)

Dietary Pattern Category	<i>n</i>	Vegetables	Fruits	Fish	Whole Grains	Sweets	Processed Meat	Refined Grains	Wine	Liquor	Beer
Healthy diet											
Low	272	14.0	13.0	4.9	116.6	48.3	61.8	7.1	2.9	130.7	23.8
Medium	272	26.2	22.4	6.9	121.3	53.9	63.6	9.5	3.9	110.5	38.8
High	271	48.7	34.4	9.8	120.4	61.2	59.6	10.5	8.9	70.7	34.0
Western diet											
Low	271	33.8	21.4	6.5	80.9	37.0	39.6	9.0	10.3	112.5	37.8
Medium	273	27.5	22.7	6.9	113.4	52.5	58.5	8.7	2.9	82.6	27.3
High	271	27.5	25.6	7.9	164.1	73.9	87.0	9.5	2.6	117.1	31.5
Alcohol drinker											
Low	272	34.5	30.5	7.1	124.0	71.0	52.4	8.7	1.7	27.1	10.1
Medium	271	27.2	20.1	6.8	116.5	51.8	59.0	9.1	3.5	57.3	22.3
High	272	27.1	19.1	7.5	117.8	40.6	73.6	9.4	10.5	227.5	64.2

Table 4. Distribution of Dietary Pattern Scores by Selected Subjects' Characteristics Among Control Subjects^a

	Symptomatic Gastroesophageal Reflux (<i>n</i>)		Smoking (<i>n</i>)			BMI		Total Energy Intake (Kcal/day)	
	Yes	No	Never	Ex-Smoker	Current smoker	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>
Healthy diet									
Low	43	229	87	116	69	23.9	0.16	2176.5	39.2
Medium	54	218	107	101	64	24.0	0.17	2347.9	45.6
High	38	233	129	96	46	23.8	0.18	2479.7	50.1
<i>P</i> value		0.17		0.004			0.70		<0.0001
Western diet									
Low	45	226	114	101	56	23.3	0.15	1825.3	33.6
Medium	38	235	101	108	64	23.9	0.19	2190.2	25.8
High	52	219	108	104	59	24.4	0.16	2989.1	43.6
<i>P</i> value		0.26		0.82			<0.0001		<0.0001
Alcohol drinker									
Low	41	231	147	85	40	23.9	0.18	2199.9	39.9
Medium	47	224	102	116	53	23.7	0.15	2185.9	39.3
High	47	225	74	112	86	24.1	0.18	2617.2	52.0
<i>P</i> value		0.72		<0.001			0.24		<0.0001

^a: Abbreviation is as follows: BMI, body mass index.

Table 5. Esophageal and Gastric Cardia Cancer Risk Associated with Dietary Patterns^{a,b}

	Controls (<i>n</i>)	Esophageal Adenocarcinoma		Esophageal Squamous-Cell Carcinoma		Gastric Cardia Adenocarcinoma	
		<i>n</i>	OR (95% CI)	<i>n</i>	OR (95% CI)	<i>n</i>	OR (95% CI)
Healthy diet							
Low	272	81	1.0	73	1.0	93	1.0
Medium	272	54	0.6 (0.4–0.98)	52	0.8 (0.5–1.3)	99	1.0 (0.7–1.4)
High	271	50	0.8 (0.5–1.3)	40	0.7 (0.4–1.2)	66	0.7 (0.5–1.1)
<i>P</i> value for trend			0.43		0.20		0.13
Western diet							
Low	271	47	1.0	52	1.0	62	1.0
Medium	273	59	1.3 (0.8–2.2)	56	0.9 (0.6–1.6)	95	1.7 (1.1–2.6)
High	271	79	1.6 (0.9–3.1)	57	0.7 (0.4–1.4)	101	1.8 (1.1–2.9)
<i>P</i> value for trend			0.13		0.33		0.04
Alcohol drinker							
Low	272	56	1.0	26	1.0	78	1.0
Medium	271	65	1.0 (0.6–1.6)	52	2.0 (1.2–3.6)	82	0.9 (0.6–1.3)
High	272	64	0.9 (0.5–1.5)	87	3.5 (1.9–6.3)	98	0.8 (0.6–1.2)
<i>P</i> value for trend			0.65		<0.0001		0.39

a: Abbreviations are as follows: OR, odds ratio; CI, confidence interval.

b: Age, sex, symptomatic gastroesophageal reflux, years of education, body mass index, smoking, physical activity, and total energy intake were also included in the regression models as covariates.

1.1–2.9, *P* value for trend = 0.04), and a modestly increased risk for esophageal adenocarcinoma (highest vs. lowest tertiles, OR = 1.6, 95% CI = 0.9–3.1, *P* value for trend = 0.13). Subjects who had the highest alcohol drinker scores had a more than threefold increased risk for esophageal squamous-cell carcinoma compared with those who had lowest scores (highest vs. lowest tertiles, OR = 3.5, 95% CI = 1.9–6.3, *P* value for trend < 0.0001).

Discussion

In this study, we used factor analysis to classify diets in the Swedish population into three major patterns. These patterns were characterized by high vegetables, tomato, fruits, fish, and poultry intake; high processed meat, red meat, sweets, high-fat dairy, and high-fat gravy intake; and high alcohol (beer and liquor) and French fries intake, respectively. The first pattern was associated with a moderately lower risk of esophageal squamous-cell carcinoma, esophageal adenocarcinoma, and gastric cardia adenocarcinoma. Subjects who scored high for the second pattern tended to have elevated risks for gastric cardia adenocarcinoma and esophageal adenocarcinoma. The third pattern was positively associated with only esophageal squamous-cell carcinoma risk.

Our study results are consistent with most results of previous findings (22–26), except one (9), that meat or fat intake increases the risk of adenocarcinoma of the esophagus or gastroesophageal junction. Most studies in Western populations also found an inverse association between intake of fresh vegetables and fruits, or nutrient intakes derived from these sources, and the risk of adenocarcinoma of the esophagus or the gastroesophageal junction (9,22–27), as well as the risk of esophageal squamous-cell carcinoma (22,24,26). We

found that a healthy diet pattern is inversely associated with all three types of cancer under study, although not statistically significant. However, the Western diet pattern seemed to be associated only with adenocarcinomas from the esophagus or gastroesophageal junction. It is reasonable to postulate that the changed dietary habits in Western populations in recent decades characterized by high intake of meat and fat may partly explain the observed increasing incidence rates of these adenocarcinomas, although the underlying mechanism is still unclear. The most possible pathway is through induction of overweight or obesity, a strong risk factor for esophageal or gastric cardia adenocarcinoma (8–12). A similar secular trend of adenocarcinoma of the lung has also been observed (28). It is thus of interest to explore also the role of dietary pattern for lung adenocarcinoma, although to the best of our knowledge none such report is available yet. Alcohol intake has been consistently demonstrated as an important and independent risk factor for esophageal squamous-cell carcinoma in Western populations (13), which is also supported by our finding that Alcohol drinker pattern is positively and dose-dependently associated with the risk of esophageal squamous-cell carcinoma. However, it should be pointed out that wine consumption has a low load on the Alcohol drinker pattern. In fact, it is also a minor component for the other two dietary patterns. Thus our present analysis cannot make a definitive conclusion about wine consumption and the risk of the cancers under study.

This study has some limitations. First, several steps in factor analysis, including grouping of different food items, determination of number of factors, and interpretation of those factors, were subjective. However, the three factors discerned in our study were similar to previous studies performed also in Swedish populations (15,16,20), and, in a recent validation study, these dietary patterns showed good repeatability and

validity (28). Second, our questionnaire included only 63 food and beverage items, and it was not practical to increase the number of questions and food items. We asked subjects to recall their dietary habits 20 yr prior to interview, and it is possible that there were some errors due to failures in memory, but it surely assures that the symptoms of esophageal and cardia cancer would not influence dietary habits. Third, the small number of females limited our ability to find gender differences, if any. Last, it should be noted that each pattern was also linked to other risk indicators such as BMI and socioeconomic status (SES). Although we adjusted for these factors (in the case of SES, for education), we cannot rule out some residual confounding. It is, however, inconceivable that such confounding could entirely explain our results.

The advantage of this study is its population-based design. The case subjects were all newly diagnosed and carefully classified according to histologic type and tumour site. Our control subjects were chosen randomly from the entire study area. Another strong point of the present study is that participation rates were high for both cases and controls.

In summary, our results suggest that a diet characterized by high intake of vegetables, tomato, fruits, fish, and poultry (labelled as healthy diet) tends to decrease the risk of esophageal squamous-cell carcinoma, esophageal adenocarcinoma, and gastric cardia adenocarcinoma, whereas a diet with high consumption of processed meat, red meat, sweets, high-fat dairy, and high-fat gravy (named Western diet) increases the risk of gastric cardia and esophageal adenocarcinomas. The dietary pattern characterized by high alcohol (beer and liquor) intake significantly increases the risk of squamous-cell carcinoma of the esophagus.

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Appendix. Definition of the Food Groups Used in the Dietary Pattern Analysis

Food groups	Items
Vegetables	Green salads, cauliflower, white cabbage, red cabbage, spinach, carrot, onion, leek, garlic
Tomato	Tomato
Fruits	Citrus fruits, apple, pear, banana, plums
Whole grains	French toast bread, crisp bread, rye bread, oatmeal, bran
Refined grains	Rice, macaroni, spaghetti, pancakes, waffles
Cereal	Porridge (oatmeal, rice, corn flour, semolina), infant cereal, cereal/muesli
Low-fat dairy	Low fat milk, sour milk
High-fat dairy	Whole milk, milk powder, cheese, cream, ice cream
High-fat gravy	Gravy made from the remaining cooking fat
Dressing sauce	Bechamel sauce, béarnaise sauce
Fish	Herrings, cod, flat, hake, whiting, haddock, turbot, salmon, white fish, eel, pike, perch, burbot
Poultry	Chicken
Red meat	Meat ball, pork, beef, liver, minced meat
Processed meat	Smoked salted pork, Falu sausage, hamburgers, hot dogs, blood sausage
Eggs	Fried eggs, boiled eggs, omelette
Potatoes	Boiled potatoes, baked potatoes
French fries	French fries, fried potatoes
Sweets	Buns, Danish pastries, cookies, sweet biscuits, tarts, cakes, chocolate, jam, marmalade, fruit sauce
Juice	Fruit juice
High energy drinks	Fruit syrup, soft drinks
Nuts	Nuts
Tea	Tea
Coffee	Coffee
Beer	Beer (different proofs)
Wine	Wine
Liquor	Liquor (different proofs)