Nutrient Patterns and Risk of Squamous Cell Carcinoma of the Esophagus: a Factor Analysis in Uruguay

EDUARDO DE STEFANI[1], PAOLO BOFFETTA[2], RENATO B. FAGUNDES[3], HUGO DENEO-PELLEGRINI[1], ALVARO L. RONCO[4], GISELLE ACOSTA[1] and MARÍA MENDILAHARSU[1]

[1]*Grupo de Epidemiología, Departamento de Anatomía Patológica, Hospital de Clínicas, Facultad de Medicina, Montevideo, Uruguay;*
[2]*International Agency for Research on Cancer, Lyon, France;*
[3]*Universidad de Porto Alegre, Brazil;*
[4]*Departamento de Epidemiología, Sección de Radioterapia Hospital Pereira Rossell, Montevideo, Uruguay*

Abstract. *Background: Squamous cell carcinoma of the esophagus is a common disease, with an age-standardized incidence rate of 55 cases per 100,000 persons in the northern counties of Uruguay. These rates are comparable to those observed in Iran and China. Materials and Methods: In order to contribute to the clarification of the etiology of this lethal disease, a case–control study which included 234 cases and 936 controls, frequency matched for age, sex and residence, was conducted. Factor analysis (principal components) was conducted on the controls and three factors were retained, high-fat, carbohydrates and antioxidants. These nutrient patterns were submitted to multiple logistic unconditional regression in order to estimate the odds ratios of esophageal cancer. Results: The nutrient patterns (labeled as high-fat, carbohydrates and antioxidants) were significantly associated with the risk of esophageal squamous cell cancer. Whereas the high-fat and carbohydrates patterns were directly associated with an increased risk of esophageal cancer, the antioxidants pattern was strongly protective (OR 0.39, 95% CI 0.23-0.66). Conclusion: In squamous cell carcinoma of the esophagus an antioxidant dietary pattern is protective, probably due to its action against oxidative stress while high-fat and carbohydrates patterns are associated with an increased risk which may be due to the meat and sodium content, respectively.*

Uruguay is a high-risk country for esophageal cancer, in particular in the northern provinces, bordering with Brazil (age-adjusted incidence rate adjusted to the world population of 55.8 per 100, 000 men) (1).

Most studies on the role of diet in the etiology of squamous cell carcinoma of the esophagus have focused on foods and food groups (2-33). According to Willett and Buzzard (34), foods include essential dietary constituents, major energy sources, additives, agricultural chemical contaminants, microbial toxin contaminants, inorganic contaminants, chemicals formed in the cooking or processing of food, natural toxins and other natural compounds. The focus on foods for etiological research has several practical advantages (34). In fact, epidemiological analyses based on foods are generally most directly related to dietary recommendations with public health importance.

On the other hand, the relationship with the etiology of a particular cancer type is strengthened when an association with overall intake of a nutrient is observed (34). Several studies on diet and esophageal cancer have analyzed the role of dietary constituents in this malignancy (2-3, 14, 24-33). Our group has conducted case–control studies on diet and squamous cell carcinomas (2, 5, 11, 23, 32-33), but, with three exceptions (2, 32-33), nutrients were not included in the analyses. However, these three studies suffered from low statistical power, since the number of cases was rather low.

Since the pioneer studies of Pearson (35) and Spearman (36), factor analysis has emerged as a powerful tool for reducing numerous variables into a few factors. Although the initial studies were related to psychology and psychological tests, the method rapidly expanded to social sciences, economic problems and health conditions. More recently, factor analysis has been used for nutrition and, particularly, for the role of nutrition in cancer (37). Factor analysis has been used to explore the role of food groups and nutrients in esophageal, gastric and lung cancer (38-43). Although most of the studies have been concerned with foods, two studies analyzed the role of specific nutrients (38, 43). All the studies used the principal

Correspondence to: Dr. Eduardo De Stefani, Avenida Brasil 3080 dep 402, 11300 Montevideo, Uruguay. Tel: +598 2 708 23 14, e-mail: estefani@adinet.com.uy

Key Words: Factor analysis, esophageal cancer, nutrients, bioactive substances. Uruguay.

components factor analysis, although the study of Slattery *et al*. (44) compared their results with those obtained with the maximum likelihood method. Finally, all the analyses were exploratory and were not attempts to use confirmatory analyses. Perhaps the main reason for conducting exploratory analyses was due to the fact that the role of diet in cancer is largely unknown. Two of the studies explored food patterns in relation to squamous cell carcinoma of the esophagus, with mostly similar results (41-42).

In this study using the principal components method, the role of nutrients and bioactive substances in squamous cell carcinoma of the esophagus was explored in the high-risk country of Uruguay. To our knowledge, this is the first study on factor analysis and nutrients in esophageal cancer.

Materials and Methods

Selection of cases. In the time period 1996-2004, all newly diagnosed and microscopically confirmed squamous cell carcinoma of the esophagus cases admitted for diagnosis and treatment in the four public hospitals located in Montevideo were considered eligible for this study. All the cases were symptomatic. An initial number of 239 cases were identified through the admissions records. Five patients refused the interview, leaving a final total of 234 patients (response rate 97.9%) including 184 males and 50 females. Regarding subsite, tumors of the middle third represented 50% of the total, followed by lesions of the lower third of the esophagus (32%) and lesions of the upper third (18%). The study included 200 cases previously analyzed in our last study on the role of vegetables and fruits in squamous cell carcinoma of the esophagus (23), which did not examine the role of dietary nutrients.

Selection of controls. Over the same time period and in the same hospitals, all patients hospitalized due to non-neoplastic conditions which were not related to smoking and drinking and without recent changes in their diets were considered as potential controls. This was a collective decision after agreement between the International Agency for Reasearch on Cancer (IARC) and the Epidemiology Group of the Pathology Department (EGP). The initial number of patients was 1,043. Eleven of them refused the interview, leaving 1,032 eligible controls (response rate 98.9%). From this pool, 936 patients (736 men and 200 women) were frequency matched to the cases for age (ten-year intervals), sex and residence (Montevideo, other provinces). The patients presented the following conditions: abdominal hernia (248 patients, 26.5%), eye disorders (168, 18.0%), prostate hypertrophy (146, 15.6%), benign breast diseases (75, 8.0%), fractures (75, 8.0%), diseases of the skin (48, 5.1%), varicose veins (37, 4.0%), acute appendicitis (36, 3.9%), hydatid cyst (32, 3.4%), injuries (30, 3.2%), blood disorders (21, 2.2%) and urinary stones (20, 2.1%).

Interviews and questionnaire. All the interviews were conducted face-to-face shortly after admission by two trained social workers. No proxy interviews were accepted. Cases and controls were administered with a structured questionnaire which included the following sections: sociodemographics; a complete occupational history based on jobs and their duration; family history of cancer among first-degree relatives (mother, father, sisters, brothers); self-reported height and weight five years before the date of the interview; a complete history of tobacco smoking (age at start, age at stopping, number of cigarettes smoked per day, type of tobacco, type of cigarette); a complete history of alcohol drinking (age at start, age at stopping, number of glasses drunk per day, type of beverage); a complete history of mate drinking (age at start; age at stopping, number of liters drunk per day, temperature of the beverage); a complete history of coffee drinking; a complete history of tea drinking and a food frequency questionnaire (FFQ) on 64 items. The participants were asked to report their consumption over the five years preceding admission. This FFQ allowed the estimation of total energy intake and was considered as representative of the usual diet of Uruguayans. The FFQ was tested for reproducibility (45).

Dietary constituents included in the factor analysis. The following dietary constituents and bioactive substances were analyzed: total protein, saturated fat, monounsaturated fat, polyunsaturated fat, cholesterol, fiber, vitamin C, total carotenoids, vitamin E, vitamin B6, vitamin B12, thiamine, riboflavin, folate, starch, glucose, fructose, flavonoids, phytosterols, glutathione from meat, glutathione from vegetables, glutathione from fruits, nitrates, nitrites, calcium, iron and sodium. The dietary constituents were calculated using two local tables of the chemical composition of foods (46, 47). The only exception was the carotenoids which were estimated using a foreign table, the Mangels *et al*. database (48). All the nutrients and bioactive substances were energy-adjusted by the residuals method and categorized in sixtiles following the distribution of the controls (34).

Statistical methods. Factor analysis was conducted using the control group. The principal components method was used in order to be consistent with other studies. Three factors were retained and loadings are showed in the factor matrix (49-51). According to Kline (51), loadings higher than 0.39 are considered significant. The factors were labeled according to their content of high loadings (either positive or negative). Since the factors were correlated, they were rotated using the oblimin oblique method. In order to retain the significant factors, the Scree plot was used (50). In order to define a simple structure, the principles of Thurstone (52) were followed, suggesting that the number of zero loadings per factor would be at least equal to the number of factors and the simple structure would be replicable in other studies. The scored patterns were obtained according to the regression method of Thomson (53). These scored factors were correlated with demographics, smoking, alcohol drinking, mate drinking and food groups using the Spearman method.

The odds ratios of squamous cell carcinoma of the esophagus for the scored patterns were estimated by unconditional multiple logistic regression (54). The basic model included the following variables: age (categorical, five strata); sex; residence (two strata); urban/rural status (two strata); birthplace (categorical, three strata); education (categorical, three strata); body mass index (categorical, four strata); tobacco smoking (categorical, eight strata); alcohol drinking (categorical, five strata); mate consumption (categorical, four strata); total energy intake (continuous) and the scored patterns. Since scored patterns were conditional on each other, the three patterns were included in the model (40).

Tests for trend were performed after entering the categorical variables as ordinal in the same model. Departure from the multiplicative model of interaction was determined by applying the likelihood ratio test statistic. An alpha level of 0.05 was used as an indicator of statistical significance and, accordingly, 95% CIs were reported. All the *p*-values were derived from two-sided statistical tests. All the calculations were conducted with the STATA programme (55).

Results

The distribution of cases and controls by sociodemographics and selected risk factors are shown in Table I. As a result of the matched design, age, sex and residence were identical. Moreover, the distribution of controls and cases was very similar for urban/rural status, hospital, interviewer, year of diagnosis and monthly income. On the other hand, the percentage of cases born in the northeastern provinces was significantly higher compared with the controls ($p<0.001$) and the cases were significantly less educated than the controls ($p<0.001$). The cases were significantly leaner than the controls ($p<0.001$), but they consumed quite similar amounts of total energy ($p=0.13$). The cases smoked significantly more than the controls ($p<0.001$) and drank alcohol in much higher quantities than the controls ($p<0.001$). In addition, the cases drank more mate than controls ($p<0.001$). Finally, the cases consumed much lower amounts of fresh vegetables and fruits than the controls ($p<0.001$).

The factor-matrix loadings among the controls is shown in Table II. Factor 1 showed high positive loadings for total protein, saturated fat, monounsaturated fat, polyunsaturated fat, cholesterol, pyridoxine, vitamin B12, meat glutathione, and calcium. For this reason it was labeled as the high-fat factor. Factor 2 was characterized by high loadings for starch, dietary fiber, thiamine, riboflavin, iron and sodium and was labeled as the carbohydrates pattern. Finally, factor 3 displayed high loadings of glucose, fructose, total carotenoids, vitamin C, vitamin E, folate, glutathione from fruits, flavonoids, phytosterols, nitrates and calcium and was labeled as the antioxidants pattern. The sampling frequency of the model was very good (0.92) and 87% of the total variance was explained. Furthermore, the communalities were close to one in numerous variables suggesting the adequacy of the model. All the factors showed four or more zero loadings.

The correlations between several of the variables and the nutrient patterns are shown in Table III. The high-fat pattern showed significant positive correlations with residence outside Montevideo, rural residence, black tobacco smoking, hand-rolling smoking, alcohol drinking, mate consumption, total energy intake, red meat, dairy foods and desserts. On the other hand, this pattern was inversely associated with education. The carbohydrates pattern displayed significant positive correlations with male gender, rural residence, all smoking variables, alcohol drinking, mate consumption, total energy intake, cooked vegetables and grains (rho=0.84). Finally, the antioxidants pattern showed inverse associations with smoking and alcohol drinking and positive associations with vegetables, fruits and total vegetables and fruits (rho=0.78).

The odds ratios of esophageal carcinoma for the scored nutrient patterns are shown in Table IV. The high-fat pattern was positively associated with a risk of squamous cell carcinoma of the esophagus (OR for the highest category *versus* the lowest one 2.49, 95% CI 1.21-5.12, *p*-value for trend=0.008). The carbohydrates pattern was directly associated with esophageal carcinoma (OR 2.43, 95% CI 1.23-4.82, *p*-value for trend=0.02). Finally, the antioxidants pattern displayed an inverse association with a reduction in risk of 41% (OR 0.39, 95% CI 0.23-0.66, *p*-value for trend=0.001).

Discussion

This study identified nutrient patterns which were associated either with an increased or a decreased risk of esophageal cancer, thus confirming the suitability of this approach to study dietary determinants of this disease.

The use of nutrients by factor analysis has been questioned by Martinez *et al.* (56), who suggested that this approach should be limited to foods and/or food groups. Nevertheless, it is our opinion that the inclusion of nutrients could enlarge the knowledge about esophageal cancer and other malignancies. In fact, nutrients obviously derive from foods, thus providing complementary information on the etiology of esophageal cancer. Furthermore, in the present study bioactive substances, such as flavonoids, phytosterols and reduced gluthathione among other constituents, were also included.

Although nutrients are not extremely useful for public health planning, we considered that research on these constituents and esophageal carcinoma risk, using exploratory factor analysis, could be worthwhile in order to replicate case–control and prospective studies in the field (2-23), reducing large datasets to a small number of factors.

There are limitations in the use of factor analysis. These are not related to the method *per se*, but to incorrect use by researchers and are mainly related to the construction of a reliable database. Therefore it is necessary to be cautious and to include in the study variables strongly associated with the disease under consideration. Furthermore, the principal components approach should be scale dependent and the variables should be expressed in commensurable units (55).

The high-fat pattern in the present study was rich in different types of fat, total protein and vitamin B12. In fact, the role of fats in the etiology of esophageal squamous cell cancer has not been extensively studied. On the other hand, meat, the main source of fat, has been subjected to several studies, mostly contradictory. Whereas Launoy *et al.* (26) presented an inverse association, which was significant, our

Table I. *Distribution of cases and controls by sociodemographics and selected risk factors.*

Variable	Category	Cases No.	Cases %	Controls No.	Controls %	Global p-value
Age (years)	40-49	19	8.1	76	8.1	
	50-59	46	19.7	181	19.7	
	60-69	75	32.1	300	32.1	
	70-79	71	30.3	284	30.3	
	80-89	23	9.8	92	9.8	1.00
Gender	Males	184	78.6	736	78.6	
	Females	50	21.4	200	21.4	1.00
Residence	Montevideo	92	39.3	368	39.3	
	Other	142	60.7	568	60.7	1.00
Urban/rural	Urban	174	74.4	689	73.6	
	Rural	60	25.6	247	26.4	0.82
Birthplace	Montevideo	58	24.8	290	31.0	
	South	101	43.2	473	50.5	
	North	75	32.0	173	18.5	<0.001
Hospital	Cancer	79	33.8	312	33.3	
	Pasteur	94	40.2	373	39.9	
	Clinicas	37	15.8	148	15.8	
	Maciel	24	10.2	103	11.0	0.99
Interviewer	MC	100	42.7	399	42.6	
	AL	134	57.3	537	57.4	0.98
Year of diagnosis	1996-1999	118	50.4	470	50.2	
	2000-2004	116	49.6	466	49.8	0.95
Education (yrs)	0-2	78	33.4	231	24.7	
	3-5	100	42.7	342	36.5	
	6-17	56	23.9	363	38.8	<0.001
Income (dollars/month)	<=146	92	39.3	357	38.1	
	147+	87	37.2	362	38.7	
	Unknown	55	23.5	217	23.2	0.91
Family history of ESCC	No	226	96.6	924	98.7	
	Yes	8	3.4	12	1.3	0.02
Body mass index	<=23.3	92	39.3	234	25.0	
	23.4-25.2	53	22.7	238	25.4	
	25.3-27.6	48	20.5	236	25.2	
	27.7+	41	17.5	228	24.4	<0.001
Total energy	<=1863	54	23.1	234	25.0	
	1864-2230	44	18.8	234	25.0	
	2231-2594	68	29.1	234	25.0	
	2595+	68	29.1	234	25.0	0.13
Smoking	Never smokers	48	20.5	345	36.9	
Former (years since stopping)	20+	17	7.3	114	7.9	
	10-19	15	6.4	72	7.7	
	1-9	33	14.1	102	10.9	
Current (cigarettes/day)	1-19	32	13.7	188	20.1	
	20-29	45	19.2	75	8.5	
	30+	44	18.8	40	4.3	<0.001
Alcohol drinking (ml/ethanol/day)	Never drinkers	73	31.2	422	45.1	
	1-60	45	19.2	252	26.9	
	61-120	48	20.5	134	14.8	
	121-240	38	16.2	88	9.4	
	241+	30	12.8	40	4.3	<0.001
Mate drinking (liters/day)	Never drinkers	11	4.7	111	11.9	
	0.01-0.99	47	20.1	255	27.2	
	1.00-1.99	126	53.8	417	44.6	
	2.00+	50	21.4	153	16.3	<0.001
Vegetables and fruits (servings/year)	<=348	92	39.3	234	25.0	
	349-541	66	28.2	234	25.0	
	542-851	47	20.1	234	25.0	
	852+	29	12.4	234	25.0	<0.001
No. patients		234	100.0	936	100.0	

Table II. *Factor-loadings matrix among controls.*

Nutrient	Factor 1	Factor 2	Factor 3	Communality
Protein	0.74	0.31	0.06	0.86
Saturated fat	0.96	–0.00	–0.05	0.91
Monounsaturated fat	0.97	0.02	–0.08	0.93
Polyunsaturated fat	0.74	0.26	0.00	0.76
Cholesterol	0.82	0.01	0.04	0.70
Starch	–0.07	0.94	–0.05	0.82
Dietary fiber	–0.15	0.93	0.10	0.84
Fructose	–0.12	–0.15	0.83	0.64
Glucose	–0.08	–0.15	0.88	0.72
Carotenoids	0.02	0.16	0.60	0.44
Vitamin C	0.04	0.15	0.71	0.60
Vitamin E	0.24	0.19	0.64	0.68
Folate	0.32	0.08	0.68	0.73
Vitamin B6	0.54	0.11	0.40	0.65
Vitamin B12	0.97	–0.09	–0.07	0.87
Thiamine	–0.03	0.95	–0.02	0.88
Riboflavin	0.44	0.58	0.03	0.75
Meat glutathione	0.92	–0.07	–0.05	0.78
Vegetables glutathione	–0.02	0.37	0.48	0.44
Fruit glutathione	–0.03	–0.18	0.84	0.66
Flavonoids	–0.11	0.07	0.61	0.37
Plant sterols	0.04	–0.04	0.82	0.69
Nitrates	0.03	0.34	0.52	0.49
Nitrites	0.37	0.49	0.20	0.64
Calcium	0.55	–0.20	0.54	0.65
Iron	0.35	0.73	–0.04	0.83
Sodium	0.28	0.72	–0.03	0.73
Variance (%)	0.33	0.27	0.27	

Sampling frequency =0.92. Total variance explained (including error variance) =0.87.

Table III. *Spearman correlations between several variables and score patterns.*

Variables	Factor 1	Factor 2	Factor 3
Age (years)	–0.03	–0.04	0.07
Gender	–0.09	–0.24	–0.01
Residence	0.13	0.06	0.05
Urban/rural status	0.19	0.10	0.04
Birthplace	0.18	0.03	0.06
Education (years)	–0.13	–0.06	0.02
Body mass index	–0.06	–0.08	–0.02
Smoking intensity	0.08	0.13	–0.09
Smoking duration	0.05	0.11	–0.11
Type of tobacco	0.10	0.16	–0.04
Type of cigarette	0.10	0.14	–0.07
Alcohol drinking	0.13	0.12	–0.08
Mate consumption	0.17	0.12	0.03
Total energy intake	0.67	0.61	0.37
Red meat	0.79	0.18	0.07
Poultry	0.03	–0.02	0.14
Fish	–0.03	–0.01	0.21
Processed meat	0.34	0.20	0.05
Dairy foods	0.34	0.22	0.16
Eggs	0.27	0.15	0.17
Desserts	0.16	0.09	0.20
Total grains	0.18	0.84	0.01
Fresh vegetables	0.04	0.09	0.42
Cooked vegetables	0.28	0.43	0.41
Total vegetables	0.25	0.41	0.56
Citrus fruits	0.09	–0.02	0.47
Other fruits	0.06	0.03	0.60
Total fruits	0.09	0.02	0.74
Vegetables & fruits	0.09	0.06	0.78

earlier studies suggested that barbecued and boiled meat were directly associated with an increased risk of esophageal cancer and that salted meat was a strong risk factor (2, 11). While salted meat could increase the risk of esophageal cancer through its content of exogenous nitrosamines (11, 57), the mechanisms with barbecued meat appear to be related to the presence of heterocyclic amines and benzopyrene resulting from the cooking method.

Among the different types of fat, only polyunsaturated fat and its component linoleic acid were associated with a three-fold increase in risk in a previous study on nutrients and esophageal cancer (58). This finding merits further analysis. A previous Swedish study conducted by factor analysis showed high loadings for processed meat and red meat (41). These foods loaded in the so-called "Western diet" and this pattern was positively associated with esophageal adenocarcinoma but not with squamous cell carcinoma of this site. Similarly, in the previous Uruguayan study related to food patterns, diets which have high loadings for red meat and high-fat foods were inversely associated with risk of squamous cell carcinoma of the esophagus (42). Nevertheless, these associations were nonsignificant. Thus, the evidence of a possible increased risk associated with high consumption of meat and fat is controversial.

The carbohydrates pattern was characterized by high positive loadings for starch, fiber, thiamine, riboflavin, iron and sodium. This factor was strongly correlated with total grain intake and presented an elevated risk of squamous cell carcinoma of the esophagus. In fact, some grains such as those found in white bread have been associated with an increased risk of esophageal cancer in previous studies. On the other hand, polenta and pasta were mainly protective. The sodium intake, which showed a high loading in this pattern, was directly associated with risk of squamous cell carcinoma of the esophagus (OR 2.3, 95% CI 1.4-3.8) in a previous study. Castellsagué *et al*. (8) found an increased risk of esophageal cancer with salt consumption in their pool analysis. Therefore, salt and sodium appear to be risk factors for esophageal cancer.

The antioxidants pattern was inversely associated with risk of esophageal cancer. This pattern showed high loadings for fructose and glucose, markers of fruit intake. The vitamins

Table IV. *Odds ratios of esophageal squamous cell carcinoma for scored patterns.*

Pattern	Quartile	Cases/Controls	OR[a]	95% CI	OR[b]	95 % CI
High-fat	1	33/234	1.0	reference	1.0	reference
	2	47/234	1.37	0.84-2.25	1.21	0.68-2.15
	3	60/234	1.69	1.04-2.75	1.44	0.76-2.70
	4	94/234	2.95	1.83-4.76	2.49	1.21-5.12
		p-value for trend	<0.001		0.008	
Carbohydrates	1	32/234	1.0	reference	1.0	reference
	2	52/234	1.62	0.99-2.67	1.86	1.06-3.26
	3	69/234	2.14	1.31-3.48	1.98	1.08-3.64
	4	81/234	2.50	1.51-4.14	2.43	1.23-4.82
		p-value for trend	<0.001		0.02	
Antioxidants	1	79/234	1.0	reference	1.0	reference
	2	57/234	0.58	0.39-0.87	0.64	0.41-1.01
	3	60/234	0.56	0.38-0.84	0.61	0.38-0.96
	4	38/234	0.29	0.18-0.46	0.39	0.23-0.66
		p-value for trend	<0.001		0.001	

[a]Age and sex-adjusted. [b]Adjusted for age, gender, residence, urban/rural status, birthplace, body mass index, total energy intake, smoking status, years after stopping, number of cigarettes/day among current smokers, alcohol drinking and mate consumption.

and bioactive chemicals vitamin C, vitamin E, folate, total carotenoids, flavonoids and phytosterols are characterized by acting against oxidative stress (11-12, 17, 23, 33). This pattern was strongly correlated with consumption of vegetable and fruit, well-known protective foods in the mechanism of esophageal carcinogenesis. Therefore, it was not unexpected that this pattern was inversely associated with risk of squamous cell carcinoma of the esophagus.

Our study, as other case–control studies, had limitations. Perhaps the strongest limitation was related to recall bias and the possible differential misclassification of exposure. On the other hand, our study had several strengths. Firstly, the study was carefully designed; secondly, the statistical power was reasonable although the number of cases, particularly of females, was somewhat limited; and thirdly, both series of participants (cases and controls) showed high response rates.

In summary, the present study identified three nutrient patterns designated as high-fat, carbohydrates and antioxidants. Whereas the antioxidants pattern was clearly defined, the other patterns were more debatable. The role of linoleic acid in the high-fat factor could explain its effect in esophageal cancer. Similarly, in the carbohydrates pattern, sodium might play a role. Nevertheless, strong statements concerning the effect of these patterns in the etiology of squamous cell carcinoma of the esophagus should be avoided since the role of broad groups of nutrients has been studied in only two studies on gastric and lung cancer (38, 43).

Acknowledgements

This study was supported by a grant from the International Agency for Research on Cancer.

References

1 Vassallo JA, De Stefani E, Barrios E and Ronco A: Incidencia del Cancer en el Uruguay-1991. Comisión Honoraria de Lucha contra el Cáncer, pp. 72-75, Montevideo, Barreiro & Ramos, 1996.

2 De Stefani E, Deneo-Pellegrini H, Boffetta P and Mendilaharsu M: Meat intake and risk of squamous cell esophageal cancer: a case–control study in Uruguay. Int J Cancer *82*: 33-37, 1999.

3 Tuyns AJ, Riboli E and Doornbos G: Diet and oesophageal cancer in Calvados (France). Nutr Cancer *9*: 81-92, 1987.

4 Victora CG, Muñoz N, Day NE, Barcelos LB, Peccin DA and Braga N: Hot beverages and oesophageal cancer in southern Brazil: a case–control study. Int J Cancer *39*: 710-716, 1987.

5 De Stefani E, Muñoz N, Estève J, Vasallo A, Victora CG and Teuchmann S: Mate drinking, alcohol, tobacco, diet, and esophageal cancer in Uruguay. Cancer Res *50*: 426-431, 1990.

6 Castelletto R, Castellsagué X, Muñoz N, Iscovich J, Chopita N and Jmelnitsky A: Alcohol, tobacco, diet, mate drinking, and esophageal cancer in Argentina. Cancer Epidemiol Biomarkers Prev *3*: 557-564, 1994.

7 Rolon PA, Castellsagué X, Benz M and Muñoz N: Hot and cold mate drinking and esophageal cancer in Paraguay. Cancer Epidemiol Biomarkers Prev *4*: 595-605, 1995.

8 Castellsagué X, Muñoz N, De Stefani E, Victora CG, Castelletto R and Rolon PA: Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. Int J Cancer *88*: 658-664, 2000.

9 Ward MH, Sinha R, Heinman EF, Rothman N, Markin R, Weisenburger DD, Correa P and Hahm SH: Risk of adenocarcinoma of the stomach and esophagus with meat cooking method and doneness preference. Int J Cancer *71*: 14-19, 1997.

10 Cheng KK, Day NE, Duffy SW, Lam TH and Fox M: Pickled vegetables in the aetiology of oesophageal cancer in the Hong Kong Chinese. Lancet *339*: 1314-1318, 1992.

11 De Stefani E, Deneo-Pellegrini H, Ronco AL, Boffetta P, Brennan P, Muñoz N, Castellsagué X, Correa P and Mendilaharsu M: Food

groups and risk of squamous cell carcinoma of the oesophagus: a case–control study in Uruguay. Br J Cancer *89*: 1209-1214, 2003.

12 Bosetti C, La Vecchia C, Talamini R, Simonato L, Zambon P, Negri E, Trichopoulos D, Lagiou P, Bardini R and Franceschi S: Food groups and risk of squamous cell esophageal cancer in Northern Italy. Int J Cancer *87*: 289-294, 2000.

13 Levi F, Pasche C, Lucchini F, Bosetti C, Franceschi S, Monnier P and La Vecchia C: Food groups and oesophageal cancer in Vaud, Switzerland. Eur J Cancer Prev *9*: 257-263, 2000.

14 Tzonou A, Lipworth L, Garidou A, Signorello LB, Hsieh C-C and Trichopoulos D: Diet and risk of esophageal cancer by histologic type in a low-risk population. Int J Cancer *68*: 300-304, 1996.

15 Cook-Mozaffari PJ, Azordegan F, Day NE, Ressicaud A, Sabai C and Aramesh B: Oesophageal cancer studies in the Caspian littoral of Iran: results of a case–control study. Br J Cancer *39*: 293-309, 1979.

16 Sharp L, Chilvers CED, Cheng KK, McKinney PA, Logan RFA, Cook-Mozaffari P, Ahmed A and Day NE: Risk factors for squamous cell carcinoma of the oesophagus in women: a case–control study. Br J Cancer *85*: 1667-1670, 2001.

17 Terry P, Lagergren J, Hanen H, Wolk A and Nyrén O: Fruit and vegetable consumption in the prevention of oesophageal and cardia cancers. Eur J Cancer Prev *10*: 365-369, 2001.

18 Franceschi S, Bidoli E, Baron AE and La Vecchia C: Maize and risk of cancers of the oral cavity, pharynx, and esophagus in northeastern Italy. J Natl Cancer Inst *82*: 1407-1411, 1990.

19 Yu Y, Taylor PR, Li J-Y, Dawsey SM, Wang W, Blot WJ and Shen Q: Retrospective cohort study of risk factors for oesophageal cancer in Linxian, People's Republic of China. Cancer Causes Control *4*: 195-202, 1993.

20 Guo W, Blot WJ, Li J-Y, Taylor PR, Liu BQ, Wang W, Wu YP, Zheng W, Dawsey SM, Li B and Fraumeni JF Jr: A nested case–control study of oesophageal and stomach cancers in the Linxian nutrition intervention trial. Int J Epidemiol *23*: 444-450, 1994.

21 Sauvaget C, Nagano HJ, Hayashi M, Spencer E, Shimizu Y and Allen N: Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Lifespan Study. Br J Cancer *88*: 689-694, 2003.

22 Tran GD, Sun X-D, Abnet CC, Fou J-H, Dawsey SM, Dong Z-W, Mark SD, Qiao X-L and Taylor PR: Prospective study of risk factors for esophageal and gastric cancer in the Linxian General Population Trial cohort in China. Int J Cancer *113*: 456-463, 2004.

23 De Stefani E, Boffetta P, Deneo-Pellegrini H, Ronco AL, Correa P and Mendilaharsu M: The role of vegetable and fruit consumption in the aetiology of squamous cell carcinoma of the oesophagus: A case–control study in Uruguay. Int J Cancer *116*: 130-135, 2005.

24 Ziegler RG, Morris LE, Blot WJ, Pottern LM, Hoover R and Fraumeni JF, Jr: Esophageal cancer among black men in Washington DC. II Role of nutrition. J Natl Cancer Inst *67*: 1199-1206, 1981.

25 Brown LM, Swanson CA, Gridley G, Swanson GM, Silverman DT, Greenberg RS, Hayes RB, Schoenberg JB, Pottern LM, Schwartz AG, Liff JM, Hoover R and Fraumeni JF Jr: Dietary factors and the risk of squamous cell esophageal cancer among black and white men in the United States. Cancer Causes Control *9*: 467-474, 1998.

26 Launoy G, Milan Ch, Day NE, Pienkowski MP, Gignoux M and Faivre J: Diet and squamous-cell cancer of the oesophagus: a French multicentre case–control study. Int J Cancer *76*: 7-12, 1998.

27 Decarli A, Liatti P, Negri E, Franceschi S and La Vecchia C: Vitamin A and other dietary factors in the etiology of esophageal cancer. Nutr Cancer *10*: 29-37, 1987.

28 Gao Y-T, McLaughlin JK, Gridley G, Blot WJ, Ji B-T, Dai Q and Fraumeni JF Jr: Risk factors for esophageal cancer in Shanghai, China. II Role of diet and dietary constituents. Int J Cancer *58*: 197-202, 1994.

29 Hu J, Nyrén O, Wolk A, Bergström R, Yuen J, Adami H-O, Guo L, Li H, Huang G, Xui X *et al*: Risk factors for oesophageal cancer in Northeast China. Int J Cancer *57*: 38-46, 1994.

30 Tavani A, Negri E, Franceschi S and La Vecchia C: Risk factors for esophageal cancer in lifelong nonsmokers. Cancer Epidemiol Biomarkers Prev *3*: 387-392, 1994.

31 Zhang Z-F, Kurtz RC, Yu G-P, Sun M, Gargon N, Karpeh M, Fein JS and Harlap S: Adenocarcinomas of the esophagus and gastric cardia: The role of diet. Nutr Cancer *27*: 298-309, 1997.

32 De Stefani E, Brennan P, Boffetta P, Ronco AL, Mendilaharsu M and Deneo-Pellegrini H: Vegetables, fruits, related dietary antioxidants and risk of squamous cell carcinoma of the esophagus: A case–control study in Uruguay. Nutr Cancer *28*: 23-29, 2001.

33 De Stefani E, Ronco A, Mendilaharsu M and Deneo-Pellegrini H: Diet and risk of the upper aerodigestive tract. II Dietary nutrients. Oral Oncol *35*: 22-26, 1999.

34 Willett W and Buzzard IM: Foods and dietary constituents. *In*: Nutritional Epidemiology. Second edition. Willett W (ed.). Oxford University Press, New York, pp. 18-32, 1998.

35 Pearson K: On lines and planes of closest fit to systems of points in space. Phil Mag *6*: 559-572, 1901.

36 Spearman C: General intelligence, objectively determined and measured. Am J Psychol *15*: 201-293, 1904.

37 Randall, E, Marshall, JR, Brasure, J and Graham S: Dietary patterns and colon cancer in western New York. Nutr Cancer *18*: 265-276, 1992.

38 Palli D, Russo A and Decarli A: Dietary patterns, nutrient intake and gastric cancer in a high-risk area of Italy. Cancer Causes Control *12*: 163-172, 2001.

39 De Stefani E, Correa P, Boffetta P, Deneo-Pellegrini H, Ronco AL and Mendilaharsu M: Dietary patterns and risk of gastric cancer: a case–control study in Uruguay. Gastric Cancer *7*: 211-220, 2004.

40 Balder HF, Goldbohm RA and van den Brandt PA: Dietary patterns associated with male lung cancer risk in the Netherlands Cohort Study. Cancer Epidemiol Biomarkers Prev *14*: 483-490, 2005.

41 Bahmanyar S and Ye W: 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. Nutr Cancer *54*: 171-178, 2006.

42 De Stefani E, Boffetta P, Ronco AL, Deneo-Pellegrini H, Correa P, Acosta G and Mendilaharsu M: Exploratory factor analysis of squamous cell carcinoma of the esophagus in Uruguay. Nutr Cancer *60*: 188-195, 2008.

43 De Stefani E, Boffetta P, Ronco AL, Deneo-Pellegrini H, Acosta G, Mendilaharsu M: Nutrient patterns and risk of lung cancer: a factor analysis in Uruguayan men. Lung Cancer, accepted February 2008, in press.

44 Slattery ML, Boucher KM, Caan BJ, Potter JD and Ma K-N: Eating patterns and risk of colon cancer. Am J Epidemiol *148*: 4-16, 1998.

45 Ronco AL, De Stefani E, Boffetta P, Deneo-Pellegrini H, Acosta G and Mendilaharsu M: Food patterns and risk of breast cancer: a factor analysis study in Uruguay. Int J Cancer *119*: 1672-1678, 2006.
46 Mazzei ME, Puchulu MR and Rochaix MA: Tabla de Composición Química de Alimentos. Segunda Edición. CENEXA, pp. 119-127, Buenos Aires, 1995.
47 Ministerio de Salud Pública: Guías Alimentarias Basadas en Alimentos de Uruguay. Dirección General de la Salud, MSP, Montevideo, Uruguay, pp. 20-35, 2005.
48 Mangels AR, Holden JM, Beecher GR, Forman MR and Lanza E: Carotenoid content of fruits and vegetables: An evaluation of analytic data. J Am Diet Assoc *93*: 284-296, 1993.
49 Harman HH: Modern Factor Analysis. Third edition. Chicago: University of Chicago Press, pp. 300-335, 1976.
50 Kim J-O and Mueller CW: Factor Analysis. Statistical Methods and Practical Issues. Sage University Paper N°14, California, SAGE publications, Inc. USA, pp. 44-45, 1978.
51 Kline P: An Easy Guide to Factor Analysis. Routledge, New York, USA, pp. 64-69, 2002.
52 Thurstone LL: Multiple Factor Analysis: Development and Expansion of Vectors of the Mind. Chicago: University of Chicago Press, pp. 14-18, 1947.
53 Thomson GH: The Factorial Analysis of Human Ability. London: University of London Press, pp. 154-159, 1951.
54 Breslow NE and Day NE: Statistical Methods in Cancer Research. Volume 1-The Analysis of Case–Control Studies. IARC Scientific Publications Nº 32. Lyon, pp. 202-205, 1980.
55 StataCorp: Stata Statistical Software. Release 9. College Station, Texas, pp. 229-250, 2005.
56 Martínez ME, Marshall JR and Sechrest L: Invited commentary: Factor analysis and the search for objectively. Am J Epidemiol 148: 17-19, 1998.
57 Craddock VM: Aetiology of oesophageal cancer: some operative factors. Eur J Cancer Prev *1*: 89-103, 1992.
58 De Stefani E, Ronco AL, Boffetta P, Deneo-Pellegrini H, Acosta G, Correa P and Mendilaharsu M: Nutrient intake and risk of squamous cell carcinoma of the esophagus: A case–control study in Uruguay. Nutr Cancer *56*: 149-157, 2006.

Received January 23, 2008
Revised May 2, 2008
Accepted May 16, 2008