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Dietary Indicators of Laryngeal Cancer Risk[1]

Carlo La Vecchia,[2] Eva Negri, Barbara D'Avanzo, Silvia Franceschi, Adriano Decarli, and Peter Boyle

Istituto di Ricerche Farmacologiche "Mario Negri," Via Eritrea 62, 20157 Milan, Italy [C. L. V., E. N., B. D.]; Institute of Social and Preventive Medicine, University of Lausanne, 1005 Lausanne, Switzerland [C. L. V.]; Inter-University Consortium of Lombardy for Automatic Data Processing (CILEA), 20090 Segrate, Milan, Italy [E. N.]; Aviano Cancer Centre, 33081, Pordenone, Italy [S. F.]; Institute of Medical Statistics, University of Milan, National Cancer Institute, 20133 Milan, and Institute of Statistics, University of Trento, 38100 Trento, Italy [A. D.]; and Unit of Analytical Epidemiology, The International Agency for Research on Cancer, 69372 Lyon, France [P. B.]

ABSTRACT

The relationship between frequency of intake of a selected number of indicator foods and the risk of laryngeal cancer was investigated in a case-control study conducted in northern Italy on 110 males with histologically confirmed cancer of the larynx and 843 controls in the hospital for acute, nonneoplastic or respiratory diseases. Significant direct associations were observed with tobacco [relative risk (RR) = 5.8 for current *versus* never smokers] and alcohol (RR = 2.3 for the upper *versus* lower tertile of consumption), while the frequency of consumption of three food items was inversely related with laryngeal cancer risk. These were fish (RR = 0.6 for the upper tertile), green vegetables (RR = 0.4), and fresh fruit (RR = 0.3). Multiple logistic regression analysis, including simultaneously major nondietary covariates and various food items, suggested that the strongest and most consistent protective effect was given by fruit. These findings can be generally interpreted as an indication that a "poorer" diet is related to a raised risk of laryngeal cancer, although the confirmed observation that fruit appears to be the main protective dietary factor against cancers of the upper respiratory and digestive tract is of potential interest and may suggest useful etiological clues. Dietary findings were similar in different strata of alcohol and tobacco consumption.

INTRODUCTION

Tobacco and alcohol are the major identified risk factors for laryngeal cancer (1–4). Other factors, however, may play some independent role on laryngeal carcinogenesis, such as occupational exposures (5–7) and diet (8–10). This is indirectly suggested by the observation that social class indicators are strongly and inversely related with laryngeal cancer rates (1, 7), but only scanty direct epidemiological evidence is available.

A study based on the Roswell Park Memorial Institute dataset (8) (338 laryngeal cancer patients, 359 controls without cancer or respiratory or digestive diseases) found a relative risk, adjusted for cigarettes and alcohol, of 3 for the lowest level of vitamin A intake and of 2.5 for vitamin C. A population-based case-control study from Texas (9) suggested that the protection conferred by vitamin A could be restricted to its precursor, carotene, while no association was found with retinol or total vitamin A. The authors pointed out that the apparent contradiction with the Roswell Park Memorial Institute dataset can be explained by the fact that that study measured vitamin A intake derived almost exclusively from carotene. Another case-control study conducted in Uruguay (10) found a relative risk of 2.7 for "never" as compared with "daily" consumption of fruits and some indication of an inverse trend with vegetables, too (RR[3] = 1.7 for "infrequent" *versus* "daily" consumption).

In order to gain further information on the issue, we studied the relationship between a few selected indicator foods and laryngeal cancer risk, using data from a case-control study conducted in Milan, northern Italy. This is a relatively high mortality area from larynx cancer, by both national and European standards (11, 12).

SUBJECTS AND METHODS

The data were derived from an ongoing study of neoplasms of the upper digestive and respiratory tract based on a network of teaching and general hospitals from the Greater Milan area, northern Italy, whose general design and methods have already been described (13). Recruitment of cases of laryngeal cancer started in January 1987, and the present analysis is based on data collected before April 1989.

Trained interviewers identified and questioned cases and controls using a structured questionnaire. Next-of-kin interviews were not admitted. On the average, less than 3% of eligible subjects (cases and controls) refused to be interviewed. Information was collected on sociodemographic factors, personal characteristics, and habits; use of tobacco and alcohol in various forms; coffee and other methylxanthine-containing beverages; related personal and medical history; and specific drug use history. Questions on alcohol included the number of days per week each type of alcoholic beverage (wine, beer, and spirits) was consumed, the average number of drinks per day, and the duration of habit in years. Data were also collected on the usual frequency of consumption per week before the onset of symptoms of the disease which led to hospital admission of ten indicator foods, and simple subjective scores (low, intermediate, high) were used as measures of use of whole meal bread or pasta and of various fats in condiments (butter, margarine, oil). Thus, a total of 17 food items were considered in this report. The interviews were repeated by telephone after a few weeks time in a subsample of approximately 10% of cases and controls, to check reliability and reproducibility of the questionnaire and interviews.

Cases. The cases studied were patients under the age of 75 yr who had been admitted for histologically confirmed laryngeal cancer to the National Cancer Institute and the Ospedale Maggiore of Milan, which includes the four largest teaching and general hospitals in Milan. Only incident cases (*i.e.*, whose diagnoses were made within the year before interview) were considered. A total of 110 male cases, aged 33 to 74 yr (median age, 60 yr), were interviewed.

Controls. The control group comprised men below age 75, admitted to the same network of hospitals for acute conditions other than neoplastic, respiratory, or diseases related to alcohol or tobacco consumption. A total of 843 subjects (aged 24 to 74 yr; median age, 55 yr) were interviewed. Of these, 29% were admitted for traumatic conditions, 15% had nontraumatic orthopedic diseases (mostly low back pain and disc disorders), 43% acute surgical diseases, and 13% other miscellaneous illnesses, such as ear, nose, and throat, skin, or dental disorders.

The catchment area of cases and controls was comparable: 82% of the cases and 83% of the controls came from the same region, Lombardy, and in large proportion from the highly industrialized Greater Milan area, which includes about 50% of the population of the entire region; 8% of the cases and 10% of the controls were from other northern Italian regions; 10% of the cases and 6% of the controls were from central or southern Italy.

Data Analysis and Control of Confounding. Frequencies of consumption of various food items were (*a*) considered separately and (*b*) used to derive indices of retinoid (preformed vitamin A) and carotenoid (provitamin A), using tables of nutrient values issued by the Italian Depart-

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[2] To whom requests for reprints should be addressed, at "Mario Negri" Institute for Pharmacological Research, Via Eritrea 62, 20157 Milan, Italy.

[3] The abbreviations used are: RR, relative risk; CI, confidence interval.

ment of Agriculture (14). Total alcohol consumption was computed assuming a comparable ethanol content in each type of drink (*i.e.*, 150 ml of wine = 330 ml of beer = 30 ml of spirits = approximately 12 ml of pure alcohol). Measures of food item consumption were subdivided into three levels including (as far as possible) the same number of cases and controls combined (approximate tertiles). Although there is no published research showing that using the basis of controls or cases plus controls in the definition of tertiles has any statistical advantage, since in this study there were about 8 controls per case, this would introduce only negligible differences in any of the analyses. RRs of laryngeal cancer, together with their 95% approximate CIs (15), were first computed from the data stratified for decade of age by means of the usual Mantel-Haenszel procedure (16). Significance was assessed by means of the linear trend test described by Mantel (17).

To account simultaneously for the potential confounding effect of major identified covariates, multiple logistic regression was used (18), including terms for age, area of residence (Lombardy *versus* others), education, and smoking. Similar results were obtained using social class (defined according to occupation of the head of the household) instead of education as the socioeconomic indicator. Finally, since various food items may act to confound each other, models were produced including various dietary factors simultaneously, whose effect remained significant after the analyses described above.

RESULTS

Age, education, and smoking habits are considered in Table 1. The cases were older than the comparison group, of lower social class, and less educated (only 5.5% reported 12 or more yr of school compared with 24% of the controls); they were also more likely to be smokers (the age-adjusted RRs were 5.4 for current and 9.8 for heavy smokers).

Table 2 gives the distribution of laryngeal cancer cases and controls according to approximate frequency tertiles of 17 selected foods and beverages. There was no significant association with milk and dairy products, eggs, various types of meats and fats, whole meal foods, and coffee. Three items (fish, green vegetables, and fruit) showed significant inverse trends, which were particularly strong for vegetables and fruit, with RR for the upper tertile of 0.3 and 0.2. Alcohol was the sole item to show a significant positive association; the RR for the upper tertile, corresponding to more than six drinks per day, was 2.3 (95% CI = 1.4–3.6), although there was no risk below that level.

The four items showing significant associations with laryngeal cancer were further included in two series of multiple logistic regression equations, including (*a*) the major nondietary covariates and (*b*) both nondietary variables and food items. The results obtained are presented in Table 3. The risk estimate for the upper tertile of alcohol intake decreased appreciably (from 2.3 to 1.8), probably on account of the high correlation between alcohol and smoking. Nonetheless, the relative risk for alcohol was still of borderline significance. None of the estimates for other foods was materially changed after multivariate analysis, and the inverse trends in risk remained highly significant for vegetables and fruit.

Models based on simultaneous inclusion of various food items are harder to interpret, on account of problems of collinearity and hence increased standard errors. However, they suggest that the strongest and most consistent association was with fruit, while those with fish and green vegetables were somewhat reduced.

Table 4 considers the relationship of laryngeal cancer with fresh fruit in separate strata of never plus exsmokers and current smokers and in three levels of alcohol consumption. There was no appreciable interaction with tobacco and alcohol, and the pattern of risk was consistent across various strata. Thus, the relative risks for exposure to both factors were grossly elevated (*i.e.*, approximately 7-fold for low fruit and smoking combined and 5-fold for low fruit and high alcohol intake).

Table 1 *Distribution of 110 cases of laryngeal cancer and 843 controls according to age, education, and smoking habits: Milan, Italy, 1987–1989* [a]

	Larynx cancer		Controls	
	No.	%	No.	%
Age (yr)				
<45	5	4.5	183	21.7
45–54	23	20.9	259	30.7
55–64	56	50.9	249	29.5
65–74	26	23.6	152	18.0
Education (yr)				
<7	78	71.6	376	44.9
7–11	25	22.9	260	31.1
≥12	6	5.5	201	24.0
Smoking habits				
Never smokers	8	7.3	212	25.1
Exsmokers	24	21.8	210	24.9
Pipe/cigar smokers	1	0.9	9	1.1
Cigarette smokers				
<15/day	5	4.5	127	15.1
15–24/day	36	32.7	173	20.5
≥25/day	36	32.7	112	13.3

[a] For some variables, the sum of strata does not add up to the total because of missing values.

DISCUSSION

This study confirmed that various aspects of diet may influence the risk of laryngeal cancer. Besides the well-known positive association with alcohol, three of the indicator foods investigated (fish, green vegetables, and fruit) showed a significant inverse relation with laryngeal cancer risk. The subjects in the upper tertile of fish consumption had about half the risk, and those in the highest tertile of fruit or vegetables had about one-third the risk of those in the corresponding lowest tertile. The strongest and most consistent protective effect was observed with fruit, and the protection persisted after allowance for other food items using multivariate analysis.

Previous studies observed a strong protective effect of fruit intake on cancers of the mouth or pharynx and esophagus. For instance, in a large population-based case-control study of oral and pharyngeal cancer conducted in several areas of the United States, McLaughlin *et al.* (19) found a significant protection of fruits and several nutrients with fruits as a major source (vitamin C, carotene, fiber), but no association with vegetables or with the same nutrients in vegetables. Likewise, in case-control studies of esophageal cancer conducted in Italy (20), France (21), and Brazil (22), the apparent protection was greater for fruit, although some inverse relationship was observed with measures of vegetable intake, too. With specific reference to laryngeal cancer, De Stefani *et al.* (10) in a case-control study from Uruguay found greater protection by fruit than by vegetable consumption.

It is difficult, however, to speculate on which component of fruit is specifically protective against neoplasms of the upper digestive and respiratory tract, or whether a diet rich in fruit simply represents an aspecific favorable indicator.

Our questionnaire measured a number of important sources of vitamin A in the Italian diet and, although based on a very restricted selection of indicator foods, may be sufficient to test the association between disease and intake of this specific micronutrient (23, 24). Carotenoids, but not retinoids, were inversely related with laryngeal cancer risk, but the relation was

Table 2 *Relation of laryngeal cancer risk with frequency of use of selected indicator foods and beverages: Milan, Italy, 1987–1989*

Food or beverage	Frequency of consumption (no. of cases:no of controls)[a] 1 (low)	2 (intermediate)	3 (high)	Relative risk estimates[b] 1 (low)	2 (intermediate)	3 (high)	χ^2_1 (trend)
Milk	51:317	20:87	39:439	1[c]	1.5	0.5	3.54
Meat	39:254	48:263	23:326	1[c]	1.3	0.5	2.59
Liver	88:668	22:175		1[c]	0.9		0.08
Eggs	29:260	52:411	29:172	1[c]	1.1	1.6	1.30
Ham and salami	43:290	34:256	33:297	1[c]	1.0	0.9	0.08
Fish	58:319	33:343	19:181	1[c]	0.5	0.6	5.63[d]
Cheese	32:280	33:218	45:345	1[c]	1.3	1.4	2.23
Carrots	53:403	34:214	23:226	1[c]	1.2	0.8	0.28
Green vegetables	55:330	47:325	8:188	1[c]	0.9	0.3	8.31[e]
Fresh fruit	46:181	38:262	26:390	1[c]	0.5	0.2	34.52[e]
Whole meal bread or pasta	97:673	13:170		1[c]	0.6		3.21
Butter	50:442	60:401		1[c]	1.5		3.37
Margarine	93:705	17:138		1[c]	1.2		0.23
Oil	10:59	87:605	13:179	1[c]	1.0	0.8	1.59
Total fat score	34:314	65:353	11:176	1[c]	1.7	0.5	0.36
Alcohol	44:433	23:221	43:189	1[c]	1.0	2.3	13.44[e]
Coffee	33:304	33:226	44:313	1[c]	1.4	1.4	2.12

[a] For some variables, the sum of strata does not add up to the total because of missing values.
[b] Mantel-Haenszel estimates adjusted for age in decades.
[c] Reference category.
[d] $P < 0.05$.
[e] $P < 0.01$.

Table 3 *Multivariate relative risks of laryngeal cancer in relation to selected indicator foods: Milan, Italy, 1987–1989*

Food item	Model	Relative risk estimates for frequency of consumption 1 (low)	2 (intermediate)	3 (high)	χ^2_1 (trend)
Fish	A[a]	1[b]	0.6	0.5	5.75[c]
	B[d]	1[b]	0.6	0.6	4.68[c]
Green vegetables	A[a]	1[b]	1.1	0.2	8.08[e]
	B[d]	1[b]	1.4	0.4	2.15
Fresh fruit	A[a]	1[b]	0.5	0.3	26.12[e]
	B[d]	1[b]	0.5	0.3	16.61[e]
Alcohol	A[a]	1[b]	1.1	1.8	4.10[c]
	B[d]	1[b]	0.9	1.7	2.56

[a] Derived from multiple logistic regression models including terms for age, area of residence, education, and smoking (defined as in Table 1).
[b] Reference category.
[c] $P < 0.05$.
[d] Derived from models including simultaneously the above nondietary covariates and all food items listed in this table (including alcohol).
[e] $P < 0.01$.

Table 4 *Relative risks[a] of laryngeal cancer in relation to fresh fruit in separate strata of tobacco and alcohol consumption: Milan, Italy, 1987–1989*

Fresh fruit	Tobacco: Never/exsmokers (n = 32)	Tobacco: Current smokers (n = 78)	Alcohol (drinks/day): <2 (n = 44)	2–6 (n = 23)	>6 (n = 43)
Low	1[b]	1[b]	1[b]	1[b]	1[b]
Intermediate	0.5	0.7	0.4	0.5	1.2
High	0.3	0.3	0.3	0.2	0.3

[a] Mantel-Haenszel estimates were adjusted for age and, respectively, tobacco or alcohol.
[b] Reference category.

weaker than with measures of fruit consumption. Probably, therefore, the association was not specific, but simply reflected a generally poorer nutritional status in the cases. Along the same lines, an explanation could be offered for the apparent protection with fish intake, also observed for oropharyngeal cancer in the study by McLaughlin *et al.* (19).

There are some obvious limitations to the present study, such as the restricted food list, the absence of subsite distinction within the larynx (3), the fact that it was not population based, or the choice of hospital controls, which is still open to debate in relation to the analysis of lifestyle habits or diet. Interviewer bias is conceivable, since the diagnosis was known to the interviewers who both identified and questioned cases and controls. However, the role of diet in laryngeal cancer risk had not gained widespread attention in Italy and was only one of the issues of the study, hence reducing the scope for differential interviewers' attention and subjects' recall by cases and controls. Further, participation was practically total, cases and controls came from very comparable catchment areas, and the results were consistent across separate strata of the major diagnostic categories of the controls. In relation to confounding, the role of dietary factors persisted after allowance for major potential distorting factors, including smoking, alcohol, and social class indicators, and the protection was consistent and comparable across strata of alcohol and tobacco.

In conclusion, therefore, we are inclined to interpret these findings, as well as previous epidemiological evidence, as an indication that a generally less affluent diet may be related to laryngeal cancer, although the confirmed observation that fruit appears to be an important protective factor against cancers of the upper respiratory and digestive tract (10, 19–22) is of potential interest and may suggest useful etiological clues.

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