Dietary consumption patterns and laryngeal cancer risk

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Abstract

*We conducted a case-control study to investigate the effect of diet on laryngeal carcinogenesis. Our study population was made up of 140 participants—70 patients with laryngeal cancer (LC) and 70 controls with a non-neoplastic condition that was unrelated to diet, smoking, or alcohol. A food-frequency questionnaire determined the mean consumption of 113 different items during the 3 years prior to symptom onset. Total energy intake and cooking mode were also noted. The relative risk, odds ratio (OR), and 95% confidence interval (CI) were estimated by multiple logistic regression analysis. We found that the total energy intake was significantly higher in the LC group (*p *< 0.001), and that the difference remained statistically significant after logistic regression analysis (*p *< 0.001; OR: 118.70). Notably, meat consumption was higher in the LC group (*p *< 0.001), and the difference remained significant after logistic regression analysis (*p *= 0.029; OR: 1.16). LC patients also consumed significantly more fried food (*p *= 0.036); this difference also remained significant in the logistic regression model (*p *= 0.026; OR: 5.45). The LC group also consumed significantly more seafood (*p *= 0.012); the difference persisted after logistic regression analysis (*p *= 0.009; OR: 2.48), with the consumption of shrimp proving detrimental (*p *= 0.049; OR: 2.18). Finally, the intake of zinc was significantly higher in the LC group before and after logistic regression analysis (*p *= 0.034 and *p *= 0.011; OR: 30.15, respectively). Cereal consumption (including pastas) was also higher among the LC patients (*p *= 0.043), with logistic regression analysis showing that their negative effect was possibly associated with the sauces and dressings that traditionally accompany pasta dishes (*p *= 0.006; OR: 4.78). Conversely, a higher consumption of dairy products was found in controls (*p *< 0.05); logistic regression analysis showed that calcium appeared to be protective at the micronutrient level (*p *< 0.001; OR: 0.27). We found no difference in the overall consumption of fruits and vegetables between the LC patients and controls; however, the LC patients did have a greater consumption of cooked tomatoes and cooked root vegetables (*p *= 0.039 for both), and the controls had more consumption of leeks (*p *= 0.042) and, among controls younger than 65 years, cooked beans (*p *= 0.037). Lemon (*p *= 0.037), squeezed fruit juice (*p *= 0.032), and watermelon (*p *= 0.018) were also more frequently consumed by the controls. Other differences at the micronutrient level included greater consumption by the LC patients of retinol (*p *= 0.044), polyunsaturated fats (*p *= 0.041), and linoleic acid (*p *= 0.008); LC patients younger than 65 years also had greater intake of riboflavin (*p *= 0.045). We conclude that the differences in dietary consumption patterns between LC patients and controls indicate a possible role for lifestyle modifications involving nutritional factors as a means of decreasing the risk of laryngeal cancer.*

Introduction

Laryngeal cancer (LC) is the third most common malignancy of the upper aerodigestive tract, and the thirteenth most common cancer in men.[1] During the decades that followed World War II, the incidence of LC underwent a rather alarming increase, even among women, which was largely attributed to changes in women's tobacco and alcohol consumption.[2] However, these two risk factors cannot completely explain the variance in the

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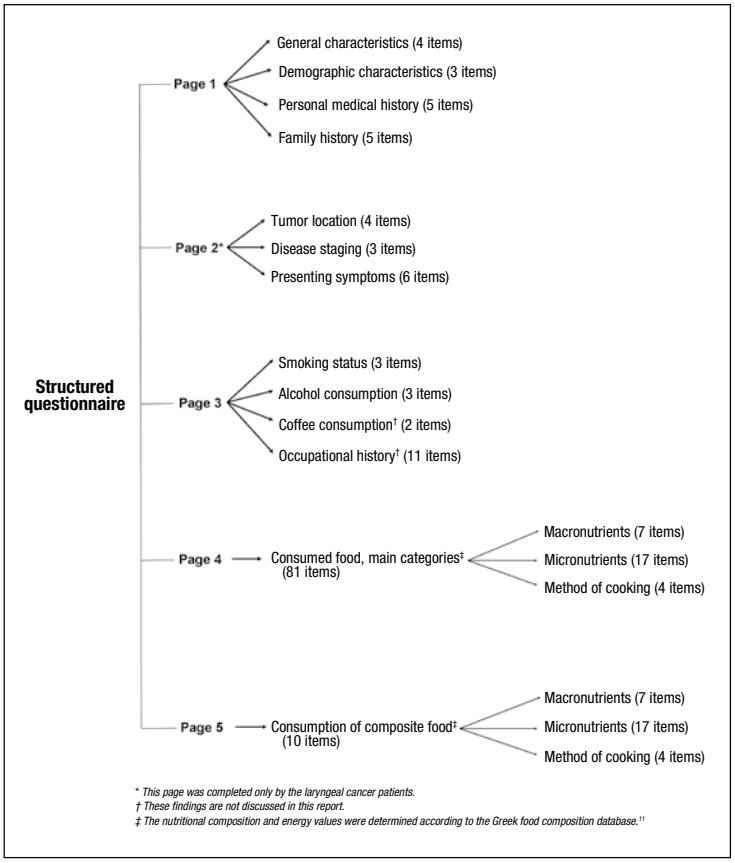

Figure. Diagram summarizes the structured questionnaire used during each participant's interview. Note that the estimate of macro- and micronutrients on the right part of pages 4 and 5 was performed after each interview.

epidemiology of LC. Other lifestyle-associated factors may play a significant role in laryngeal carcinogenesis.[3-7]

It has been reported that 35% of all cancers may be associated with diet, irrespective of their location,[8] and that at least one-third of the annual cancer deaths in the United States can be attributed to dietary factors.[9] Indeed, a positive correlation between LC and the consumption of traditional Greek/Turkish coffee was recently reported, and this correlation proved to be statistically significant after adjusting for tobacco and alcohol consumption.[10] Since the prevention of cancer is a key issue from a public health perspective, there seems to be an increasing interest in the association between LC and total energy intake and dietary habits.

In this article, we describe our study of the potential association between diet and documented squamous cell carcinoma of the larynx.

Patients and methods

We conducted a case-control study of LC over a 2-year period at the ENT Department at Hippokrateion General Hospital, a tertiary care university hospital. Our study population was made up of 140 participants—70 patients with laryngeal cancer (LC) and 70 controls with a non-neoplastic condition that was unrelated to diet, smoking, or alcohol.

LC patients. Our exclusion criteria for the LC group included the presence of nonsquamous cell carcinoma of the larynx, unrelated carcinoma/neoplasia in another organ, diabetes mellitus, and renal insufficiency. The LC group included 70 patients—65 men and 5 women with a mean age of 64.3 ± 8.8 years—who had squamous cell carcinoma of the larynx. All of these patients were enrolled in the study after histologic confirmation of the carcinoma and a few days before curative surgery. Confirmation was obtained during their inpatient preoperative workup. Three other eligible patients refused to participate in the study.

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used to assign codes to the related diagnoses. Glottic cancer (ICD-9: 161.0) was present in 29 of the 70 patients (41.4%), supraglottic cancer (ICD-9: 161.1) in 21 patients (30.0%), transglottic cancer (ICD-9: 161.8) in 19 patients (27.1%), and subglottic cancer (ICD-9: 161.2) in 1 patient (1.4%).

Controls. The 70 controls—64 men and 6 women with a mean age of 69.7 ± 10.9 years—were selected from among inpatients who were hospitalized during the same time. These patients had a non-neoplastic condition not related to diet, smoking, or alcohol consumption. Three other eligible controls declined to participate.

In the control group, 47 patients had an eye disorder (67.1%), 16 had an injury (22.9%), 2 each (2.9%) were being treated for an abdominal hernia and epistaxis, 2 were undergoing a tympanoplasty, and 1 (1.4%) had a peritonsillar abscess.

Study protocol. All 140 participants were personally interviewed by one of the authors (A.V.). They also completed a structured questionnaire that included current weight and weight 2 years earlier, residence (urban or rural), education, personal and family medical history, tobacco smoking (number of cigarettes smoked per day, number of years of smoking, and type of tobacco), alcohol drinking (number of years of drinking, number of units per day or week, and type of alcohol), coffee consumption, and a complete occupational history (figure).

There were no significant differences between the

two groups in terms of sex, medical history, weight at either benchmark, and years of education. However, the mean age of the cancer patients was lower than that of the controls by approximately 5 years (64.3 ± 8.8 vs. 69.7 ± 10.9; $p = 0.001$). In order to adjust for the significant difference, the cases and controls were subcategorized according to a cutoff value of 65 years, which represented the median age (table 1).

Table 1. Demographic characteristics, smoking, and alcohol consumption in the study participants

Variable	Cases n (%)	Controls n (%)	*p* Value
Sex			1.000
Male	65 (92.9)	64 (91.4)	
Female	5 (7.1)	6 (8.6)	
Age, yr			0.015
<65	34 (48.6)	9 (27.1)	
≥65	36 (51.43)	51 (72.9)	
Residence			0.011
Urban	25 (35.7)	41 (58.6)	
Rural	45 (64.3)	29 (41.4)	
Smoking*			<0.001
Yes	51 (72.9)	21 (30.0)	
No	1 (1.4)	25 (35.7)	
Alcohol consumption			<0.001
Yes	14 (20.0)	35 (50.0)	
No	56 (80.0)	35 (50.0)	

** 18 LC patients and 24 controls were former smokers.*

Information on diet included the mean self-reported consumption frequency of 113 different items during the 3 years prior to symptom onset, on a monthly, weekly, or daily basis. Food was subclassified into five main categories: meat, seafood, dairy products, cereals, and fruits and vegetables. All collected data were ultimately quantified as grams on a daily basis by multiplying the consumption frequency with the portion of a given food for a middle-aged person in grams.[6]

The nutritional composition and energy value of Greek composite foods, along with the respective values of the main food categories, were determined with the aid of a food composition database developed by Trichopoulou and Georga.[11] The total energy intake and the method of cooking were also noted. The latter included four dimensions: (1) the specific cooking method (stewed, traditionally slow-cooked, fried, or roasted), (2) the use of salt (salty, medium, or lightly salted), (3) the use of oil (oily, medium, or dry), and (4) the status of the food before preparation (frozen or fresh).

Statistical analysis. Statistical analysis was performed with the Statistical Package for the Social Sciences software (v. 14.0). The chi-square statistic incorporating the Yates correction was used to compare the basic characteristics of the two groups, as well as the initial positive or negative effect of each food category. The Mann-Whitney *U* test was employed to investigate distributional differences of the categorical variables between cases and controls. The consumed nutrients in both groups were weighed against the related energy intake to neutralize any confounding effect of the latter on the results.

The results were further analyzed by logistic regression. The forward stepwise method was used to select variables to be maintained in the final model. The dependent variables included tobacco smoking, alcohol drinking, total energy, energy with food, proteins, total fats, monounsaturated fats, polyunsaturated fats, linoleic acid, cholesterol, carbohydrates, fibers, retinol, carotenoids, thiamine, riboflavin, nicotinic acid, vitamin C, vitamin B_6, sodium, potassium, calcium, magnesium, phosphorus, iron, and zinc.

Statistical significance was accepted at $p < 0.05$. The magnitude of associations between cases and controls is illustrated as an odds ratio (OR) followed by the 95% confidence interval (CI).

Ethical considerations. The research protocol was approved by the Ethics Committee of the University of Athens prior to the commencement of data collection. Participants were asked to sign a consent form before being enrolled in the study.

Results

Before logistic regression analysis. It is no surprise that the cancer patients in the present study were more often smokers than controls ($p < 0.001$). Also, a significantly greater number of LC patients reported alcohol consumption ($p < 0.001$), and a greater number of consumed alcohol units than the controls ($p < 0.001$) (table 1).

The total energy intake was higher in the LC patients than in the controls ($p < 0.001$), mainly because of their greater alcohol consumption ($p < 0.001$). This finding remained unchanged even after adjusting for age. By

Table 2. Monthly consumption patterns among patients and controls

Food category	Cases			Controls			*p* Value
	25th %*	Median	75th %	25th %	Median	75th %	
Meat	13	16	18	11	14	16	<0.001
Seafood	2	3	4	2	2	3	0.012
Dairy products	7	9	11	7	11	13	<0.05
Cereals	15	17	19	13	17	18	0.043
Fruits and vegetables	67	80	93	73	84	96	0.161

** Percentile.*

contrast, the controls obtained more energy from food ($p = 0.034$).

With regard to the different food categories (table 2), meat consumption was higher in the LC patients ($p < 0.001$), an observation that persisted after adjusting for age ($p < 0.001$), especially with regard to red meat ($p = 0.037$) (table 3). The LC patients also tended to consume more seafood than the controls ($p = 0.012$), while a greater consumption of dairy products was found in the controls ($p < 0.05$), especially in those aged 65 years and older ($p = 0.034$). Consumption of cereals was greater in the LC patients ($p = 0.043$) (table 2).

No difference in the overall consumption of fruits and vegetables was found between the patients and controls (table 2), with the exception of the more frequent consumption of cooked tomatoes ($p = 0.039$) and cooked root vegetables ($p = 0.039$) by the LC patients and the greater consumption by the controls of leeks ($p = 0.042$) and, in those younger than 65 years, beans ($p = 0.037$). Lemon ($p = 0.037$), squeezed fruit juice ($p = 0.032$), and watermelon ($p = 0.018$) were also more frequently consumed by the controls (table 3).

At the micronutrient level, we found a greater intake of zinc and retinol among the LC patients ($p = 0.034$ and $p = 0.044$, respectively), as well as a higher intake of riboflavin (vitamin B_2) in the LC patients younger than 65 years of age ($p = 0.045$). The consumption of polyunsaturated fats ($p = 0.041$) and linoleic acid ($p = 0.008$) was also higher in the LC patients. In contrast, the controls took in more calcium ($p = 0.017$) and more fiber ($p < 0.05$) (table 3).

The mode of cooking also differed between patients and controls, with more LC patients preferring fried food (18.6 vs. 5.7%; $p = 0.036$) (table 3).

After logistic regression analysis. The positive association between tobacco smoking and LC remained statistically significant after logistic regression analysis. Current smokers had a higher incidence than those who had never smoked ($p = 0.006$; OR: 19.46; 95% CI: 2.30 to 164.70). In addition, ex-smokers had a higher incidence of LC than those who had never smoked ($p < 0.05$; OR: 9.87; 95% CI: 0.99 to 98.74) (table 4).

The association between alcohol consumption and LC remained statistically significant after the logistic regression analysis, as current drinkers still had a higher incidence of

Table 3. Dietary products consumed more often by each group

Patients	Controls
Specific foods	
Red meat ($p = 0.037$)	Rice ($p = 0.017$)
Shrimp ($p = 0.027$)	Leeks ($p = 0.042$)
Pasta ($p = 0.004$)	Beans ($p = 0.037$)*
Cooked tomatoes ($p = 0.039$)	Lemon ($p = 0.037$)
Cooked root vegetables ($p = 0.039$)	Squeezed fruit juice ($p = 0.032$)
	Watermelon ($p = 0.018$)
Specific micronutrients	
Zinc ($p = 0.034$)	Calcium ($p = 0.017$)
Retinol ($p = 0.044$)	Fiber < 0.05)
Polyunsaturated fats ($p = 0.041$)	
Linoleic acid ($p = 0.008$)	
Riboflavin ($p = 0.045$)*	
Mode of cooking	
Frying ($p = 0.036$)	

** In the <65 age category.*

LC than did nondrinkers ($p = 0.006$; OR: 3.94; 95% CI: 1.47 to 10.53) (table 4).

Meat was associated with an increased incidence of LC ($p = 0.029$; OR: 1.16; 95% CI: 1.02 to 1.33), as was seafood ($p = 0.009$; OR: 2.48; 95% CI: 1.25 to 4.92), with the consumption of shrimp proving detrimental ($p = 0.049$; OR: 2.18; 95% CI: 1.01 to 4.75). The protective effect of dairy consumption seemed to be closely associated to the related calcium intake ($p < 0.001$; OR: 0.27; 95% CI: 0.13 to 0.56). The negative effect of cereals in laryngeal carcinogenesis seemed to be associated with pasta ($p = 0.006$; OR: 4.78; 95% CI: 1.55 to 14.73), although rice actually had a protective role ($p = 0.009$; OR: 0.31; 95% CI: 0.13 to 0.75) (table 4).

With respect to other micronutrients, the LC group had a significantly higher intake of zinc ($p = 0.011$; OR: 30.15; 95% CI: 2.17 to 418.40) (table 4).

The association between the total energy intake and LC also remained statistically significant after logistic regression analysis ($p < 0.001$; OR: 118.70; 95% CI: 75.39 to 186.89) (table 4).

In terms of the mode of cooking, frying remained a significant risk factor for laryngeal carcinogenesis after applying the regression model ($p = 0.026$; OR: 5.45; 95% CI: 1.22 to 24.30) (table 4). The differences between the LC patients and controls with respect to the other methods of cooking were not statistically significant.

Table 4. Risk factors for laryngeal carcinogenesis after logistic regression analysis

Variable	*p* Value	OR (95% CI)
Tobacco		
Smoking	0.006	19.46 (2.30 to 164.70)
Not smoking	0.009	
History of previous smoking	<0.05	9.87 (0.99 to 98.74)
Alcohol	0.006	3.94 (1.47 to 10.53)
Meat	0.029	1.16 (1.02 to 1.33)
Seafood	0.009	2.48 (1.25 to 4.92)
Shrimp	0.049	2.18 (1.01 to 4.75)
Cereals		
Pasta	0.006	4.78 (1.55 to 14.73)
Rice	0.009	0.31 (0.13 to 0.75)*
Micronutrients		
Calcium	<0.001	0.27 (0.13 to 0.56)*
Zinc	0.011	30.15 (2.17 to 418.40)
Total energy	<0.001	118.70 (75.39 to 186.89)
Mode of cooking		
Frying	0.026	5.45 (1.22 to 24.30)

** Protective effect.*

Discussion

While there is no absolute consensus on how to categorize the various food groups, they are popularly classified as meat, seafood, dairy products, cereals, and fruits and vegetables.[12]

Meat. In our study, meat consumption had a detrimental effect in terms of LC incidence, and this effect persisted after adjusting for age. A similar finding was reported by De Stefani et al with respect to fresh meat consumption.[13] At the micronutrient level, we made the interesting finding that LC patients younger than 65 years of age had a greater intake of riboflavin ($p = 0.045$). Taking into account that meat represents the main source of this nutrient, it is quite possible that this finding is associated with the higher consumption of meat.

Other studies have identified consumption of meat—processed and salt-preserved meat in particular—as a strong indicator for LC cancer risk.[14-16] In contrast, Kjaerheim et al reported only a borderline increase in the relative cancer risk with frequent beef and bacon consumption.[17] Among the mechanisms that might explain meat-related carcinogenesis is a high intake of nitrosamine from salt-preserved meat.[16] The high amount of total fat intake associated with the consumption of processed meat and its products seems to exert a synergistic effect with tobacco smoking.[18]

Seafood. The greater intake of seafood by the LC patients in our study was quite interesting, as it seems to differ from the findings of previously published research. Indeed, both the International Agency for Research on Cancer's study in Southwestern Europe[7] and a case-control study by Notani and Jayant[19] found that a high intake of fish was associated with a lower risk of LC after adjustments for other known risk factors. This discrepancy might be explained by the greater preference for fried food among the LC patients in our study. One byproduct of frying is the production of heterocyclic amines, which are well known for their mutagenic activity.

In addition, the consumption of shrimp was also found to be detrimental, again possibly due to the nitrosamines associated with their preservation. However, it is interesting to note we also found a greater intake of zinc among the LC patients, even after logistic regression analysis. This finding might be closely associated with the higher consumption of seafood in our LC patients; zinc was also found to be a significant factor in a study by Bidoli et al.[20]

Dairy products. Our finding that dairy products were consumed significantly more often by the controls than by the LC patients is consistent with the finding of a study by Sapkota et al, who reported a negative association between dairy products and LC (OR: 0.38; 95% CI: 0.23 to 0.62).[21] Kawakita et al found that LC was negatively correlated with yogurt intake.[22] However, neither Kawakita et al nor Gallus et al[23] found that the consumption of milk and other dairy products was a strong risk indicator for LC.

Cereals. The significant trend toward more cereal consumption among the LC patients in our study is also consistent with the findings of others.[24] The association has been attributed to an increase in glycemic load.[25] By contrast, consumption of whole-grain cereals is considered to be a favorable risk indicator against LC.[24,26] A high degree of bread consumption has also been reported to reduce the risk of upper aerodigestive tract malignancies.[17]

While the negative effect of cereals in our study appears to be associated with pasta consumption, it is possible that the actual culprits are the sauces and dressings that traditionally accompany pasta dishes, particularly cooked tomatoes. Indeed, rice consumption was actually found to have a protective role in laryngeal carcinogenesis, which may be related to the fact that frying is not a common mode of cooking rice in Mediterranean countries.

Fruits and vegetables. Although we found no difference in the overall consumption of fruits and vegetables between our two groups, some specific fruits were significantly more often consumed by the controls; they included lemon, squeezed fruit juice, and watermelon. The protective effect of citrus fruits has been previously reported in the literature, and it has been attributed to the vitamin C component or to the fact that lemon may limit the carcinogenic effect of nitrosamines when it is squeezed directly onto cooked meat.[17,26,27] However, our study is the first to find that an increased consumption of watermelon, a fruit that is inextricably integrated into the Mediterranean diet, was protective against LC. This finding, which persisted after adjusting for age, may be associated with watermelon's flavonoid micronutrients, which have been found to have a beneficial effect in terms of LC risk.[28]

Our finding that fiber was the only component of vegetables that was taken significantly more often by the controls is also in concordance with previously reported findings.[29] Our finding that some cooked vegetables—tomatoes and edible root vegetables—were significantly more often consumed by the LC patients might be explained by the fact that these vegetables are commonly boiled, which might destroy most of their protective nutrients.

De Stefani et al found a significant decrease in LC risk associated with the consumption of raw vegetables (OR: 0.29) and for the combined intake of raw fruits and vegetables in general (OR: 0.38).[6] While they did not find that vegetables in general had a protective effect (OR: 0.57), they reported that raw tomatoes, cabbage, and beans were particularly protective against LC. Moreover, the joint effect of heavy smoking and a low intake of fruits and vegetables was associated with a significantly higher risk of LC (OR: 19.2; 95% CI: 5.7 to 64.9).

Micronutrients. At the micronutrient level, calcium intake is closely related to dairy consumption. The LC patients in our study took in significantly less calcium than the controls. Logistic regression analysis confirmed the protective role of calcium, as its inverse relationship with laryngeal carcinogenesis persisted after adjusting for age among patients older than 65 years.

Total energy intake. It should be noted that during our data analysis, we took into account the fact that total energy intake has often been related to disease risk in epidemiologic studies.[30] We did so because differences in disease incidence may also be related to metabolic efficiency, and therefore to total energy intake. In addition, since the intake of specific nutrients, particularly macronutrients, is correlated with total energy intake, these nutrients may not be causally associated with disease; they may represent a confounding effect of the total energy intake.[30]

The total energy intake in our study was indeed significantly higher in the LC patients than in the controls, primarily because of their significantly greater alcohol consumption. This finding remained statistically significant even after applying the logistic regression model. However, when adjustments for total energy intake were performed—at the nutrient level and with regard to the different food categories—the significantly higher intake of polyunsaturated fats and linoleic acid in the LC group did not remain statistically significant after logistic regression analysis.

Mode of cooking. The specific method of cooking is an independent and synergistic variable of food consumption and diet. Despite the methodologic difficulties encountered in epidemiologically assessing the related evidence,[31] previous studies have found a significantly higher risk for LC in patients with a high consumption of fried food.[5,32] This higher risk is associated with the destruction of nutrients with antioxidant properties in addition to the increased production of heterocyclic amines.[5]

Our finding that the LC patients consumed significantly more fried food than the controls remained significant even after the logistic regression analysis.

Study strengths and limitations. We used a food-frequency questionnaire to determine the mean consumption of different foods and nutrients. Self-administered dietary questionnaires have been shown to provide useful information about individual nutrient intake,[33] as the correlation coefficients for reproducibility and validity in these questionnaires indicate that they are reasonably reproducible and reliable for determining the intake of many nutrients.[34] However, it is conceivable that a recent cancer diagnosis might influence a patient's reporting. Nevertheless, the design of our study was prospective, and the design of the detailed and structured questionnaire minimized the potential recall bias, which may be present in retrospective studies.[35] In addition, heavy smokers and drinkers might have a different level of awareness of their dietary intake than those who are neither.

Another consideration is that life habits in hospital controls might be different from those in the general population, and these habits might be associated with the reasons for their hospitalization. To minimize this factor, we excluded any controls with a neoplastic disease or other disease related to diet, smoking, or alcohol consumption.

The strengths of our study also included the complete participation of both cancer patients and controls and the robust statistical analysis. Patients with recurrent LC were also excluded to eliminate the possibility of confounding lifestyle habits before and after the first diagnosis of LC.

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