

Energy, macronutrients and laryngeal cancer risk

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Background: A role for diet in laryngeal carcinogenesis has been suggested, but only a few studies have examined the potential relationship with a wide variety of macronutrients.

Patients and methods: A case–control study was conducted between 1992 and 2000 in Italy and Switzerland, including 527 incident cases of laryngeal cancer, and 1297 controls hospitalized for acute, non-neoplastic conditions. The subjects' usual diet was investigated through a validated food frequency questionnaire, including 78 foods and beverages. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional multiple logistic regression models.

Results: Cases reported higher energy intake than controls. The continuous OR for 100 kcal/day was 1.16 (95% CI 1.12–1.21) for alcohol energy, and 1.02 (95% CI 1.01–1.04) for non-alcohol energy. A significantly increased risk of laryngeal cancer was observed for animal protein (continuous OR = 1.21, 95% CI 1.03–1.41), polyunsaturated fats other than linoleic and linolenic fatty acids (OR = 1.43, 95% CI 1.19–1.70), and cholesterol intake (OR = 1.43, 95% CI 1.19–1.71). Laryngeal cancer risk was slightly reduced with increasing vegetable protein (OR = 0.75, 95% CI 0.62–0.91), sugar (OR = 0.84, 95% CI 0.71–1.00) and monounsaturated fatty acid intake (OR = 0.83, 95% CI 0.70–0.99).

Conclusions: Laryngeal cancer cases have a higher energy intake than control subjects, and report a higher intake of animal protein and cholesterol.

Key words: case–control study, diet, laryngeal cancer, nutrients, risk factors

Introduction

Although tobacco smoking and alcohol drinking are the two major determinants of laryngeal cancer risk [1, 2], a role for diet has also been suggested [3]. Fruit and vegetable consumption, and consequently antioxidant nutrients, have been associated with a reduced risk of laryngeal cancer [3, 4]. There is, however, limited evidence for other dietary correlates of laryngeal cancer [3], and only a few studies collected dietary histories detailed enough to examine the potential relationship of laryngeal cancer with a wide variety of macronutrients.

Among these, a case–control study from New York on 250 cases of laryngeal cancer and 250 population controls found an increased risk for total fat [odds ratio (OR) = 2.6], but not for protein intake, after controlling for energy intake [5]. A large, multicenter case–control study conducted in six regions of southwestern Europe, including 1147 male cases and 3057 population controls, reported no significant associations with proteins, carbohydrates or total fat, although a reduced risk was found for a high polyunsaturated/monounsaturated ratio (OR = 0.5) [6]. In a case–control study from Uruguay on cancers of the upper aerodigestive

tract, an increased risk of laryngeal cancer was found in relation to total fat (OR = 1.7), protein (OR = 1.6), and cholesterol intake (OR = 1.5) [7]. Another case–control study from the same country, including 140 laryngeal cancer cases and 420 hospitalized patients, reported increased risk of laryngeal cancer for total fat intake (OR = 3.1), and various types of fatty acids [8].

In order to provide further insight into the association between energy, various macronutrients and fatty acids and laryngeal cancer risk, we analyzed the data of a large case–control study from Italy and Switzerland, where diet was measured with an extensive and validated food frequency questionnaire (FFQ) [9, 10].

Patients and methods

A case–control study of cancer of the larynx was conducted between 1992 and 2000 in two Italian areas and in the Swiss Canton of Vaud [11].

Cases were 527 patients (478 men and 49 women, median age 61 years, range 30–79) admitted to major teaching and general hospitals in the areas under study with incident, histologically confirmed squamous-cell carcinoma of the larynx, diagnosed no longer than 1 year before the interview. Laryngeal cancer cases included 271 glottis, 117 supraglottis, four subglottis, five laryngeal cartilage, 19 overlapping lesion of larynx and 111 unspecified laryngeal cancers.

Controls were 1297 subjects (1052 men and 245 women, median age 61 years, range 31–79) admitted to the same hospitals as cases for a wide spec-

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trum of acute, non-neoplastic conditions, not related to smoking, alcohol consumption and long-term modification of diet, and frequency-matched with cases by 5-year age groups, sex and area of residence. To compensate for the rarity of laryngeal cancer in women, a control-to-case ratio of about five was chosen for females, as opposed to two for males. Twenty-seven per cent of the controls were admitted for traumas, 22% for other orthopedic disorders, 29% for acute surgical conditions, and 22% for miscellaneous other illnesses, including eye, nose, ear, skin or dental disorders.

All subjects were interviewed during their hospital stay using a structured questionnaire, administered by *ad hoc* trained interviewers. Information was collected on sociodemographic characteristics, anthropometric measures, lifestyle habits, including tobacco smoking and alcohol drinking, a personal medical history, and family history of cancer in first-degree relatives.

The subjects' diet during the 2 years before cancer diagnosis or hospital admission (for controls) was investigated through an interview-administered FFQ, proven to be satisfactorily valid [10] and reproducible [9]. This included 78 foods and beverages, as well as a range of recipes common to the study areas, grouped into seven sections: (i) bread and cereal dishes (first courses); (ii) meat and other main dishes (second courses); (iii) vegetables (side dishes); (iv) fruit; (v) sweets, desserts and soft drinks; (vi) milk, hot beverages and sweeteners; (vii) alcoholic beverages. Subjects reported the average weekly frequency of consumption of each dietary item; intakes less than once a week, but at least once a month, were coded as 0.5/week. Several questions aimed at assessing fat intake pattern were also included in the questionnaire, and used to derive quantitative estimates of intake of fats used for seasoning and cooking. A food composition database was used to calculate the composition of diet in terms of total energy and various nutrient intake [12]. As a main source of data, a large, unpublished database of approximately 3000 items was provided by the National Nutrition Institute of Rome. The composition of food items included in that database was checked according to standard methods, and values for nutrients not included in the database were derived from other sources. The composition/100 g of 1991 food items with reference to total energy intake and 90 nutrients was provided by this database.

Statistical analysis

In order to examine the effect of various macronutrients independent of total caloric intake, 'calorie-adjusted' nutrient intakes were derived using the residual method suggested by Willett and Stampfer [13]. These 'calorie-adjusted' macronutrients were then categorized into quintiles based on the distribution of controls, and corresponding ORs and 95% confidence intervals (CIs) were estimated using unconditional multiple logistic regression models [14]. All models included terms for age (5-year groups), sex, center, years of education (<7, 7–11, ≥12), body mass index (quintiles), tobacco smoking (never, ex-smoker, current smoker of <15, 15–24, ≥25 cigarettes/day), alcohol drinking (<14, 14–27, 28–55, ≥56 drinks/week, plus a dummy variable for ex-drinkers), and non-alcohol energy intake (quintiles). In alternative models, 'calorie-adjusted' macronutrients were entered as continuous variables, with a measurement unit equal to the difference between the upper cut point of the fourth quintile and that of the first one. Tests for trend were based on the likelihood ratio test between models with and without a linear term for each macronutrient. ORs according to a fully partitioned model were also computed in order to allow for mutual confounding effects of all major macronutrients [15, 16].

Results

Table 1 gives the distribution of 527 laryngeal cancer cases and 1297 controls according to age, sex, and selected covariates. By design, the proportion of women was higher in controls than in cases, and the age distribution was similar in cases and controls.

Table 1. Distribution of 527 laryngeal cancer cases and 1297 controls according to selected variables: Italy and Switzerland 1992–2000

	Cases		Controls	
	No.	%	No.	%
Sex				
Male	478	90.7	1052	81.1
Female	49	9.3	245	18.9
Age (years)				
<50	59	11.2	133	10.1
50–54	74	14.0	188	14.5
55–59	97	18.4	259	20.0
60–64	113	21.4	266	20.5
65–69	105	19.9	264	20.4
≥70	79	15.0	187	14.4
Education (years)				
<7	289	54.8	653	50.4
7–11	137	26.0	400	30.8
≥12	101	19.2	244	18.8
Smoking status ^a				
Never smokers	19	3.6	485	37.3
Ex-smokers	159	30.3	460	35.6
Current smokers				
<15 cigarettes/day	58	11.1	146	11.3
15–24 cigarettes/day	187	35.6	142	10.9
≥25 cigarettes/day	102	19.4	63	4.9
Alcohol intake (drinks/week) ^a				
0–13	58	11.1	428	33.0
14–27	76	14.5	347	26.8
28–55	176	33.6	362	27.9
≥56	214	40.8	159	12.3
Body mass index (kg/m ²)				
<23.46	157	29.8	259	20.0
23.46–25.24	96	18.2	255	19.7
25.25–26.95	95	18.0	264	20.3
26.96–29.01	90	17.1	257	19.8
≥29.02	89	16.9	262	20.2

^aThe sum does not add up to the total because of missing values.

Cases did not differ from controls in terms of education, but reported a significantly higher tobacco (OR = 19.83 for current versus never smokers) and alcohol consumption (OR = 5.91 for drinkers of eight drinks/day versus never drinkers), and tended to have a lower body mass index (OR = 1.69 for subjects in the lower as compared with the higher quintile). The difference in body mass index between cases and controls was not restricted to the time of cancer diagnosis, but was also present in young and middle ages (data not shown).

In Table 2 the comparison of cases and controls according to their energy intake is presented. Cases reported higher energy intake than controls (OR = 4.35, 95% CI 2.75–6.88 for the highest

Table 2. Odds ratios^a (OR) of laryngeal cancer and corresponding 95% confidence intervals (CI) according to the daily energy intake: Italy and Switzerland 1992–2000

	Mean energy (kcal)		Quintile of intake, OR (95% CI)				χ^2 trend	OR ^b , continuous (95% CI)
	Cases	Controls	2	3	4	5		
Total energy ^c	3023.8	2611.5	1.68 (1.04–2.72)	2.17 (1.36–3.49)	3.44 (2.16–5.47)	4.35 (2.75–6.88)	53.39 ^d	1.04 (1.03–1.06)
Alcohol energy	516.8	279.5	0.51 (0.32–0.81)	0.48 (0.31–0.74)	0.71 (0.47–1.06)	2.10 (1.46–3.02)	28.49 ^d	1.16 (1.12–1.21)
Non-alcohol energy	2507.0	2334.1	1.64 (1.05–2.56)	2.47 (1.60–3.82)	2.30 (1.49–3.56)	2.47 (1.60–3.80)	16.33 ^d	1.02 (1.01–1.04)

^aEstimates from unconditional logistic regression adjusted for sex, age, center, education, body mass index, tobacco smoking, alcohol drinking and non-alcohol energy intake. The lowest quintile is the reference category.

^bEstimate for an addition of 100 kcal/day.

^cAdjusted also for alcohol drinking.

^d $P < 0.0001$.

versus the lowest quintile of intake). Alcohol energy, which accounts for 17% of total energy in cases and 11% in controls, showed a U-shaped relationship with laryngeal cancer risk, with an increased risk only for the highest quintile of intake (OR = 2.10, 95% CI 1.46–3.02). Non-alcohol energy was still higher in cases than in controls (OR = 2.47, 95% CI 1.60–3.80), although the trend in risk was weaker than for total energy. The continuous ORs for 100 kcal/day were 1.16 (95% CI 1.12–1.21) for alcohol energy, and 1.02 (95% CI 1.01–1.04) for non-alcohol energy.

Table 3 shows the mean intake of various macronutrients, fatty acids and cholesterol among controls, and the corresponding OR. A significantly increased risk of laryngeal cancer was observed with increasing protein (OR = 1.62, 95% CI 1.08–2.43 for the highest quintile as compared with the lowest one), animal protein (OR = 1.71, 95% CI 1.16–2.52), polyunsaturated fats other than linoleic and linolenic fatty acids (OR = 2.18, 95% CI 1.48–3.21) and cholesterol intake (OR = 1.76, 95% CI 1.19–2.62). Laryngeal cancer risk was inversely related to vegetable protein intake (OR = 0.51, 95% CI 0.33–0.77). Reductions in risk, although not significant, were also found with increasing sugar (OR = 0.71, 95% CI 0.48–1.05), monounsaturated fatty acid (OR = 0.68, 95% CI 0.45–1.02) and oleic acid intake (OR = 0.72, 95% CI 0.48–1.08). The inverse relationship with monounsaturated fatty acid and oleic acid intake was reduced after including vegetables in the regression model, which are likely to be consumed with monounsaturated fats. Intake of starch, total fat, saturated fat and polyunsaturated fatty acids were unrelated to laryngeal cancer risk.

The relationships between macronutrients found to be significantly associated with laryngeal cancer risk were further examined in Table 4 in separate strata of various covariates of interest. Risk patterns were consistent across strata of sex, age, alcohol drinking and tobacco smoking, although the OR tended to be stronger in men, in heavy alcohol drinkers (≥ 28 drinks/week) and in smokers or ex-smokers for less than 20 years. Similar ORs were observed in the two major subsites of laryngeal cancer, i.e. cancers of the supraglottis including epiglottis, false cords and laryngeal ventricles, and of the glottis, including true vocal cord.

A fully partitioned model including all major macronutrients as continuous variables produced results similar to individual macronutrients. The OR relative to 100 kcal/day was 1.30 (95% CI 1.04–1.62) for protein, 0.96 (95% CI 0.90–1.04) for sugars, 1.03 (95% CI 0.97–1.08) for starch, 0.97 (95% CI 0.85–1.04) for saturated fatty acids, 0.94 (95% CI 0.79–1.18) for monounsaturated fatty acids, and 0.93 (95% CI 0.79–1.10) for polyunsaturated fatty acids.

Discussion

In this well-designed large study on laryngeal cancer, cases showed a significantly higher energy intake compared with controls. Consistent with the results of previous studies on laryngeal cancer [17, 18], as well as other upper digestive tract neoplasms [19–21], we observed a tendency for cancer cases to report low body mass index, despite their high energy intake. A plausible explanation of this paradox is that the heavy alcohol intake, which characterizes these patients, could have influenced their diet, metabolism and energy balance. Alcohol, in fact, may reduce intake and bioavailability of a variety of essential nutrients [22, 23], and several other studies showed greater energy intake, but lower than expected body weight, in drinkers as compared to non-drinkers and in alcoholics [24–26]. Tobacco smoking could also contribute with alcohol in reducing the weight of cancer cases [27, 28]. Cases may tend to report lower weight as a consequence of their weight loss after the onset and treatment for the disease [29], but this seems quite unlikely, since a tendency to leanness was often present many years before cancer diagnosis. A different recall of dietary intake by cases may also play a role, but it is also likely that cases increased their energy intake to maintain their body weight.

Although an increased energy intake was observed, no relevant associations with the major nutrients contributing to energy intake, i.e. carbohydrates and fats, were observed. Conversely, we found a slight protective effect of sugars on laryngeal cancer risk, which is not surprising, given that in this population they are derived mainly from fruit, found to be inversely related to laryngeal cancer risk [11].

Table 3. Odds ratios^a (OR) of laryngeal cancer and corresponding 95% confidence intervals (CI) according to the daily intake of selected macronutrients, fatty acids and cholesterol: Italy and Switzerland 1992–2000

Nutrient	Mean ^b (SD)	Quintile of intake, OR (95% CI)				χ^2 trend	OR ^c , continuous (95% CI)
		2	3	4	5		
Proteins (g)	95.1 (31.3)	1.30 (0.89–1.88)	1.25 (0.83–1.89)	1.75 (1.15–2.66)	1.62 (1.08–2.43)	6.89 ^d	1.13 (0.95–1.34)
Vegetable proteins (g)	32.0 (11.5)	0.81 (0.56–1.17)	0.62 (0.42–0.92)	0.59 (0.39–0.89)	0.51 (0.33–0.77)	11.86 ^e	0.75 (0.62–0.91)
Animal proteins (g)	63.1 (24.3)	0.94 (0.64–1.38)	1.26 (0.86–1.86)	1.46 (0.98–2.18)	1.71 (1.16–2.52)	10.23 ^d	1.21 (1.03–1.41)
Sugars (g)	103.9 (49.5)	0.91 (0.64–1.31)	0.71 (0.48–1.05)	0.68 (0.46–1.00)	0.71 (0.48–1.05)	4.93 ^f	0.84 (0.71–1.00)
Starch (g)	184.9 (79.9)	1.21 (0.83–1.74)	0.82 (0.54–1.23)	0.76 (0.50–1.15)	1.08 (0.72–1.62)	0.33	1.05 (0.89–1.26)
Total fat (g)	96.9 (40.7)	0.96 (0.67–1.39)	1.07 (0.73–1.57)	0.81 (0.54–1.24)	0.74 (0.48–1.14)	1.99	0.81 (0.67–0.98)
Saturated fatty acids (g)	32.1 (14.7)	0.80 (0.55–1.15)	0.77 (0.52–1.13)	0.75 (0.50–1.13)	1.03 (0.63–1.55)	0.03	0.95 (0.81–1.12)
Monounsaturated fatty acids (g)	42.8 (21.1)	0.88 (0.62–1.26)	1.06 (0.72–1.56)	0.91 (0.60–1.36)	0.68 (0.45–1.02)	2.25	0.83 (0.70–0.99)
Polyunsaturated fatty acids (g)	16.9 (10.2)	0.91 (0.62–1.36)	1.45 (0.99–2.11)	1.25 (0.85–1.83)	0.89 (0.59–1.33)	0.08	0.90 (0.75–1.09)
Oleic acid (g)	40.1 (20.4)	0.99 (0.69–1.42)	1.14 (0.77–1.68)	0.92 (0.61–1.38)	0.72 (0.48–1.08)	1.99	0.83 (0.70–0.98)
Linoleic acid (g)	14.6 (9.2)	0.81 (0.55–1.21)	1.49 (1.02–2.18)	1.14 (0.78–1.68)	0.88 (0.59–1.32)	0.05	0.89 (0.74–1.06)
Linolenic acid (g)	1.9 (1.1)	0.88 (0.59–1.29)	1.25 (0.85–1.85)	1.08 (0.72–1.60)	1.27 (0.87–1.86)	1.98	1.02 (0.89–1.16)
Other polyunsaturated fatty acids (g)	0.5 (0.2)	1.23 (0.83–1.81)	1.45 (0.98–2.14)	1.41 (0.95–2.10)	2.18 (1.48–3.21)	14.73 ^e	1.43 (1.19–1.70)
Cholesterol (mg)	356.9 (154.8)	1.01 (0.69–1.48)	1.23 (0.83–1.83)	1.32 (0.88–1.99)	1.76 (1.19–2.62)	8.80 ^d	1.43 (1.19–1.71)

^aEstimates from unconditional logistic regression adjusted for sex, age, center, education, body mass index, tobacco smoking, alcohol drinking and non-alcohol energy intake. The lowest quintile is the reference category.

^bMean intake and standard deviation (SD) among controls.

^cEstimate for a difference in intake equal to the difference between the upper cut point of fourth quintile and that of the first.

^d $P < 0.01$, ^e $P < 0.001$, ^f $P < 0.05$.

An association between total fat and laryngeal cancer has been inconsistently reported in previous studies [4], although there are some indications of a more favorable effect of mono- and polyunsaturated fats than of saturated ones on laryngeal carcinogenesis [6]. Our study gives some support to this hypothesis, showing a reduced risk of laryngeal cancer with monounsaturated, mainly oleic acid, intake. This reduction was, however, moderate, and tended to disappear after taking into account vegetables, which are likely to be consumed with monounsaturated fats (from olive oil), although this may well represent an overadjustment. We also found an increased risk with the intake of polyunsaturated fats, other than linoleic and linolenic fatty acids. These, however,

account for only about 3% of total polyunsaturated fats, and derive probably from mixed seed oils used mainly for frying.

The strongest association in our dataset was with protein intake from animal sources. A similarly increased risk in relation to protein intake has been reported in a study from Uruguay [7], although two other studies reported no relationship with protein intake [5, 6]. Only one study reported a protective effect for high protein intake: in that study, however, protein intake was measured as a score and high protein food intake was an indicator of a better/richer diet [30].

The significant association between animal protein intake and laryngeal cancer risk reflects the positive relationship found for

Table 4. Odds ratios^{ab} (OR) of laryngeal cancer and corresponding confidence intervals (CI) according to selected macronutrients, fatty acids and cholesterol, in strata of various covariates: Italy and Switzerland 1992–2000

Nutrient	Sex		Age (years)		Alcohol (drinks/week)		Tobacco smoking	
	Men	Women	<60	≥60	<28	≥28	Non-smoker ^c	Smoker ^d
Vegetable proteins	0.76 (0.63–0.93)	1.16 (0.41–3.30)	0.70 (0.52–0.95)	0.78 (0.61–1.01)	0.81 (0.57–1.15)	0.71 (0.56–0.90)	0.88 (0.57–1.38)	0.74 (0.59–0.92)
Animal proteins	1.22 (1.04–1.44)	1.01 (0.47–2.17)	1.44 (1.10–1.89)	1.10 (0.89–1.34)	1.19 (0.92–1.55)	1.22 (0.99–1.49)	1.06 (0.73–1.55)	1.29 (1.06–1.55)
Sugars	0.81 (0.66–0.98)	0.86 (0.32–2.33)	0.87 (0.66–1.14)	0.75 (0.57–0.98)	1.00 (0.69–1.46)	0.77 (0.61–0.97)	0.71 (0.43–1.15)	0.83 (0.67–1.02)
Monounsaturated fatty acids	0.83 (0.70–0.99)	1.04 (0.45–2.39)	0.86 (0.68–1.09)	0.80 (0.62–1.03)	0.87 (0.63–1.22)	0.84 (0.69–1.03)	0.96 (0.65–1.42)	0.80 (0.66–0.97)
Other polyunsaturated fatty acids	1.43 (1.19–1.73)	1.39 (0.63–3.07)	1.43 (1.10–1.86)	1.44 (1.12–1.85)	1.37 (0.99–1.89)	1.47 (1.18–1.83)	1.15 (0.77–1.72)	1.54 (1.24–1.90)
Cholesterol	1.44 (1.20–1.74)	0.95 (0.36–2.53)	1.47 (1.11–1.95)	1.40 (1.10–1.78)	1.62 (1.16–2.27)	1.33 (1.07–1.65)	1.30 (0.83–2.06)	1.47 (1.20–1.80)

^aEstimates from unconditional logistic regression adjusted for sex, age, center, education, body mass index, tobacco smoking, alcohol drinking and non-alcohol energy intake.

^bEstimate for a difference in intake equal to the difference between the upper cut point of the fourth quintile and that of the first.

^cIncludes never smokers and ex-smokers for 20 or more years.

^dIncludes smokers and ex-smokers for less than 20 years.

red meat [11], which is one of the main sources of animal proteins in this population [31]. An association between red meat consumption and laryngeal cancer was also reported in a few other investigations [8, 32, 33]. However, the results on meat are inconclusive, and no significant relationships were found for other major protein foods, such as cheese, poultry or processed meat, in our or previous studies [3]. Thus it is difficult to interpret the association between animal protein intake and laryngeal cancer, and inferences on a possible causal effect must be made with caution.

As reported in another study [7], we found a significant association with cholesterol intake. Cholesterol, found mainly in meat and eggs, is, however, strongly correlated with protein intake, and, given our results for protein, it is not surprising that similar results were found for cholesterol.

The combination of the large study size and the collection of extensive dietary information using a validated FFQ render this study one of the best to date on laryngeal cancer and diet. Further strengths include the comparable catchment areas of study subjects, the almost complete participation for both cases and controls (>90%), the collection of data on other major risk factors for laryngeal cancer, and the use of an extensive FFQ, which allows for the assessment of a broad range of macronutrients. However, as in most case–control studies, some selection and recall biases are possible [14]. A recent cancer diagnosis may influence recall of diet for the cases, although awareness of dietary hypotheses in cancer etiology are still limited in the populations studied, and the comparability of dietary history between cases and controls are improved by interviewing subjects in the same hospital settings. Dietary habits of hospital controls could be different from those of the general population and could be associated with their reasons

for hospitalization, but we paid great attention to select controls among diagnostic categories not related to diet modifications.

In conclusion, our study indicates that laryngeal cancer cases have a higher energy intake than control subjects. A positive association was found for protein from animal origin and cholesterol, whereas an inverse association was observed for sugar. No significant relationship was observed with total fat consumption, although there was an indication that monounsaturated fats—mainly oleic acid—could have a more favorable effect on laryngeal cancer than other types of fatty acids.

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