Laryngeal Cancer in Women: Tobacco, Alcohol, Nutritional, and Hormonal Factors[1]

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Abstract

Laryngeal cancer is the neoplasm with the largest male to female sex ratio in most populations. Thus, inadequate data are available on women. We analyzed several risk factors in the combined dataset from two case-control studies conducted between 1986 and 2000 in northern Italy and Switzerland. Cases were 68 women under age 79 years, with incident, histologically confirmed cancer of the larynx. Controls were 340 women, admitted to the same network of hospitals as cases, for acute, nonmalignant conditions, unrelated to tobacco and alcohol consumption. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated by logistic regression models, conditioned by age, study center and year of interview, and including terms for education, body mass index, tobacco, alcohol drinking, and nonalcohol energy intake. Laryngeal cancer was strongly associated with cigarette smoking (OR = 435.7, 95% CI: 38.2–4964.4 for smokers of ≥25 cigarettes/day) and alcohol drinking (OR = 4.3, 95% CI: 0.8–24.1 for ≥5 drinks/day). An inverse relation was found for vegetables (OR = 0.3, 95% CI: 0.1–0.9 for the highest level of consumption), fruit (OR = 0.5, 95% CI: 0.2–1.3), and olive oil (OR = 0.3, 95% CI: 0.1–0.9). Reproductive and hormonal factors were not consistently associated to laryngeal cancer risk. This investigation, based on a uniquely large number of laryngeal cancers in women, provides definite evidence that cigarette smoking is the prominent risk factor for laryngeal cancer in women, accounting for 78% of cases in this population. Alcohol and selected dietary aspects account for ~30% of cases, whereas menstrual and hormonal factors do not appear to have a consistent role in laryngeal carcinogenesis.

Introduction

Laryngeal cancer is much rarer in women than in men. The male to female sex ratio for laryngeal cancer, ranging ~10–30 in Europe (1), is the largest among all cancer sites. Not surprisingly, therefore, trends over time in mortality were unremarkable for women (2), and most published data relate to men. Among the few investigations providing data on women, a case-control study from the United States, including 56 female cases of laryngeal cancer, found a relative risk of 28.2 for smokers of >20 cigarettes/day compared with never smokers (3). Two investigations from Italy, based on 19 female cases, showed strong associations with alcohol and especially tobacco consumption (4, 5): the relative risk was 2.6 for heavy alcohol drinkers, as compared with light drinkers (4), and 24 for cigarette smokers (5). A cohort study of Swedish alcoholics found a standardized laryngeal cancer incidence ratio of 8.9 for alcoholic women (6).

Variations in laryngeal cancer incidence rates have been generally related to changes in tobacco and alcohol consumption (1, 7, 8). However, other relevant factors may be present among women (9, 10). Among these, diet may have a role in laryngeal carcinogenesis, a diet poor in fresh fruit or vegetables being associated to an increased laryngeal cancer risk (5, 11).

A role of female hormones has been suggested, but not substantiated, for several digestive tract cancers, including oral cavity and pharynx (12), esophagus (13), stomach (14), and colorectum (15). Scanty information, however, is available on any potential role of female hormones on laryngeal carcinogenesis (16), although changes in anatomical and physiological nature of the larynx in pubertal males are sex-hormone related. Along this line, Yang *et al.* (9) considered differences of laryngeal cancer sex ratio by anatomical subsite, suggesting that differential exposure to alcohol and tobacco could not by itself explain the higher sex ratio for the glottic region and that hormonal or other sex-related factors should be considered (17).

To obtain additional information about laryngeal cancer risk in women, we analyzed a dataset from two case-control studies from northern Italy and Switzerland.

Materials and Methods

This analysis is based on data from two case-control studies of laryngeal cancer, the first one conducted between 1986 and 1992 in the provinces of Milan and Pordenone (4) and the second one between 1992 and 2000 in the provinces of Pordenone and Padua, the greater Milan area, northern Italy, and the Swiss Canton of Vaud. A report based on 19 cases collected before 1991 has already been published (5).

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Table 1 Distribution of 68 female cases of laryngeal cancer and 340 controls according to age, education, and selected variables and corresponding ORs and 95% CIs. Northern Italy and Switzerland, 1986–2000

	Cases	Controls	OR[a] (95% CI)
Age (yr)			
<50	6	30	
50–54	8	40	
55–59	20	100	
60–64	9	45	
65–69	17	85	
≥70	8	40	
Education (yr)			
<6	30	234	1[b]
≥6	38	106	4.2 (1.7–10.5)
Smoking habit			
Never smoker	6	259	1[b]
Ex-smoker	7	29	4.4 (1.2–16.1)
Current smoker (cigarettes/day)	55	52	46.0 (16.1–131.2)
<15	20	38	23.7 (7.4–76.2)
15–24	28	12	135.5 (33.4–548.8)
≥25	7	2	435.7 (38.2–4964.4)
χ^2_{trend}[c]			52.75 ($P < 0.001$)
Alcohol intake (drinks/day)[d]			
<3	39	306	1[b]
3–4	16	28	1.9 (0.6–5.8)
≥5	12	6	4.3 (0.8–24.1)
χ^2_{trend}			3.49 ($P = 0.062$)
BMI (kg/m^2)[d]			
<23	36	85	1[b]
23–<26	14	111	0.5 (0.2–1.5)
≥26	17	143	0.4 (0.2–1.1)
χ^2_{trend}			3.13 ($P = 0.077$)

[a] Estimates from multiple logistic regression models, conditioned by age, year of interview and study center, and including terms for education, BMI, nonalcohol energy intake, tobacco and alcohol consumption.
[b] Reference category.
[c] Ex-smokers excluded.
[d] The sum does not add up to the total because of some missing values.

Cases considered in the present report were 68 women under 79 years (median age, 60 years), with incident, histologically confirmed laryngeal cancer (International Classification of Diseases IX: 161), admitted to the major hospitals in the areas under study. Among women admitted for acute, nonneoplastic conditions to the same network of hospitals as cases, 340 female controls (median age, 60 years) were randomly selected, frequency matched to cases by quinquennia of age, study center, and year of interview with a control-to-case ratio of 5. Twenty-three percent of the controls were admitted for nonalcohol-related traumas, 36% for nontraumatic orthopedic conditions, 15% for acute surgical disorders, and 26% for miscellaneous other illnesses (including skin, eye, or ear disorders). In both studies, the response rate was >95% for both cases and controls.

Trained interviewers collected data using structured questionnaires, including information on sociodemographic characteristics, anthropometric measures, lifestyle habits such as smoking and alcohol consumption, frequency of intake of selected foods, menstrual, reproductive, and hormonal factors, and lifelong use of oral contraceptives and menopause hormone replacement therapy. Reproducibility of the questionnaires was satisfactory (18). The questionnaire of the more recent study included a validated food frequency section based on 78 foods or groups of foods (19, 20) and from which was consequently possible to obtain estimates of the intake of several nutrients, as well as of total energy intake, using an *ad hoc* developed Italian food consumption database (21).

Table 2 ORs and 95% CIs of laryngeal cancer according to selected nutrients, foods and oils. Northern Italy and Switzerland, 1986–2000

	Categories, cases:controls, OR[a] (95% CI)			χ^2_{trend} (P)
	1 (Low)	2	3 (High)	
Retinol[b]	25:110	18:120	25:110	0.16 (0.691)
	1[c]	0.53 (0.17–1.66)	1.15 (0.41–3.22)	
Carotene[b]	31:102	19:117	18:121	0.58 (0.445)
	1[c]	0.47 (0.21–1.03)	0.74 (0.32–1.74)	
Vegetables[b]	34:91	23:132	11:117	4.74 (0.029)
	1[c]	0.67 (0.24–1.86)	0.28 (0.09–0.87)	
Fruit	30:88	38:252		
	1[c]	0.51 (0.21–1.25)		
Olive oil[d]	20:78	29:167		
	1[c]	0.28 (0.09–0.89)		
Butter[d]	10:87	39:158		
	1[c]	2.41 (0.76–7.65)		

[a] Estimates from multiple logistic regression models, conditioned by age, year of interview and study center, and including terms for education, BMI, nonalcohol energy intake, tobacco and alcohol consumption.
[b] Approximate tertiles.
[c] Reference category.
[d] Intake of olive oil and butter was available only for data collected after 1992.

Cutoff points of the tertiles, based on discrete distributions of various foods and nutrients, were computed separately for the two studies, among the distribution of both cases and controls combined. ORs[3] and the corresponding 95% CIs were estimated using multiple logistic regression models (22) conditioned by age, study center, year of interview, and including terms for education, BMI, tobacco and alcohol consumption, and nonalcohol energy intake. For the first study, the total number of portions/day was used as a proxy of nonalcohol energy intake.

Results

Table 1 shows the distribution of 68 female cases of laryngeal cancer and 340 controls according to age, education, tobacco and alcohol consumption, and BMI. Cases were significantly more educated than controls. Laryngeal cancer risk was strongly associated to cigarette smoking: compared with never smokers, the OR was 46 (95% CI: 16–131) for current smokers and rose from 24 (95% CI: 7–76) for <15 cigarettes/day to 135 (95% CI: 33–549) for smokers of 15–24 and to 436 (95% CI: 38–4964) for ≥25 cigarettes/day. The risk of laryngeal cancer was also related to alcohol drinking, although the association was appreciably less strong than for tobacco. Compared with nondrinkers or moderate drinkers (<3 drinks/day), the ORs were 1.9 (95% CI: 0.6–5.8) for 3–4 and 4.3 (95% CI: 0.8–24.1) for ≥5 drinks/day, with a trend in risk of borderline significance. A nonsignificant inverse relation was observed with BMI.

Table 2 gives the distribution of cases and controls by approximate tertiles of consumption of selected micronutrients, foods, and seasoning fats (*i.e.*, oils, butter, and other fats used as condiments) available from both questionnaires. Retinol and carotene were not associated to laryngeal cancer risk. Green vegetables and fresh fruit were inversely related to laryngeal cancer (OR for the highest level of intake was 0.3, 95% CI: 0.1–0.9 for vegetables and 0.5, 95% CI: 0.2–1.3 for fruit).

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table 3 ORs of laryngeal cancer in women and corresponding 95% CIs according to the combined effect of cigarette smoking and alcohol drinking, BMI, and vegetable consumption. Northern Italy and Switzerland, 1986–2000

	Cigarette smoking, cases:controls, OR[a] (95% CI)		
	Never and ex-smokers	<15 cigarettes/day	≥15 cigarettes/day
Alcohol drinking[b]			
<3 drinks/day	10:261	13:32	16:13
	1[c]	19.1 (6.0–60.3)	88.4 (22.5–347.2)
≥3 drinks/day	2:27	7:6	19:1
	1.3 (0.2–10.9)	20.4 (4.7–88.8)	317.9 (70.5–1434.0)
BMI[b]			
≥25 kg/m^2	3:160	5:17	13:7
	1[c]	29.0 (5.4–154.5)	157.4 (28.4–871.4)
<25 kg/m^2	10:127	14:21	22:7
	3.5 (0.9–14.0)	28.8 (6.7–122.8)	226.5 (41.6–1232.3)
Vegetable consumption			
High	7:210	11:28	16:11
	1[c]	16.9 (5.0–57.4)	96.9 (23.7–395.7)
Low	6:78	9:10	19:3
	2.9 (0.8–10.8)	26.3 (6.0–115.4)	208.1 (40.3–1075.7)

[a] Estimates from multiple logistic regression models, conditioned by age, year of interview and study center, and including terms for education, BMI, nonalcohol energy intake, and alcohol consumption.
[b] The sum does not add up to the total because of some missing values.
[c] Reference category.

Olive oil was inversely related (OR = 0.3, 95% CI: 0.1–0.9), whereas butter tended to be directly related to risk (OR = 2.4, 95% CI: 0.8–7.7).

No association was found between several other nutrients, the estimates of which were available only for the more recent study and laryngeal cancer risk. The multivariate OR for the highest tertile of intake was 1.2 (95% CI: 0.3–4.2) for lycopene, 0.5 (95% CI: 0.1–2.1) for vitamin C, 1.8 (95% CI: 0.4–8.4) for vitamin E, 1.3 (95% CI: 0.2–7.6) for vitamin B6, 0.5 (95% CI: 0.1–2.9) for folic acid, 1.2 (95% CI: 0.3–6.0) for niacin, and 0.9 (95% CI: 0.2–4.8) for monounsaturated fatty acids (data not shown).

Table 3 shows the combined effect of cigarette smoking with alcohol intake, BMI, and vegetable consumption. The OR for the combined exposure of heavy smoking with heavy alcohol drinking was 318 (95% CI: 71–1434), with low BMI was 227 (95% CI: 42–1232) and with low vegetable intake was 208 (95% CI: 40–1076). Tobacco smoking and alcohol drinking appear to have a multiplicative effect on laryngeal cancer risk (P for interaction = 0.45).

Selected menstrual, reproductive, and hormonal factors were also considered. The OR was 2.5 (95% CI: 1.0–6.0) for women with age at menarche ≥15 years compared with <13 years, and the trend in risk with age at menarche was of borderline significance. Cases reported less frequently artificial menopause (OR = 0.4; 95% CI: 0.1–1.6) and one or more abortions (OR = 0.4; 95% CI: 0.2–1.1). No material association was observed with age at menopause and number of births. The OR for ever oral contraceptive users was 1.9 (95% CI: 0.2–15.0) and that for ever hormone replacement therapy users was 0.3 (95% CI: 0.0–1.5; data not shown).

Discussion

This study, based on the largest published dataset on laryngeal cancer in women, confirms that tobacco smoking is the most important risk factor for women as for men. Results allow to quantify, more precisely than previously, the association between tobacco and laryngeal cancer risk in women. In terms of relative (although not of absolute) risk (23), tobacco appears to have a greater role in women than in men, although the small number of never smoker cases led to wide CI.

The present results also confirm that alcohol drinking has an important role in laryngeal carcinogenesis in women (6, 24, 25), but a significant association was apparent for heavy alcohol drinkers only (4, 5). Alcohol drinking is therefore a much weaker risk factor for laryngeal cancer than cigarette smoking in Italian women. This is in agreement with the findings of studies conducted in men and women in the United States (26, 27), Korea (28), and Turkey (29).

With reference to diet, this study provides additional evidence that vegetables, olive oil, and perhaps fresh fruit (11, 24, 30–32) have a favorable effect on laryngeal cancer. The apparent protection provided by olive oil gives additional evidence to its potential favorable effect on the risk of several cancer sites (33), including those of the upper digestive tract (34, 35). A nonsignificant inverse relation was observed with BMI, which is consistent with findings for oral and pharyngeal (12) and esophageal (13) cancers, and may represent an unspecific indicator of a poorer nutritional status in subjects with upper digestive and respiratory tract neoplasms.

Additional quantification of the multiplicative effect of combined exposure to cigarette smoking and alcohol drinking (10, 24, 27, 29, 36, 37) was provided by our study. The simultaneous exposure to high cigarette smoking and low vegetable consumption seems to have also a multiplicative effect on laryngeal cancer (22).

This study provides also original information about several reproductive and hormonal factors, none of which was, however, strongly related to laryngeal cancer risk (16). However, given the rarity of the disease in women, the study had a relatively low power to detect associations with these factors.

Among the strengths of this study, there are the similar catching area of cases and controls, the practically complete participation, and the allowance for several potential confounding factors. The results were similar when separate analyses were made for various diagnostic groups of controls.

In terms of population attributable risk (38, 39), tobacco smoking accounted for 78% of laryngeal cancer in women, alcohol drinking for 34%, and the combination of the two factors (based on the joint distribution of tobacco and alcohol) for 82%. For low vegetable intake, the estimated population attributable risk was 30% and for the combination of alcohol, tobacco, and vegetables was 85% (95% CI: 73–97).

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