Attributable Risk for Laryngeal Cancer in Northern Italy[1]

Alessandra Tavani,[2] Eva Negri, Silvia Franceschi, Fabio Barbone, and Carlo La Vecchia

Istituto di Ricerche Farmacologiche "Mario Negri", Via Eritrea 62, 20157 Milano, Italy [A. T., E. N., C. L. V.]; Aviano Cancer Center, 33081 Aviano (Pordenone), Italy [S. F., F. B.]; Servizio di Igiene ed Epidemiologia, Universita di Voline, Via Colugna 40, 33100 Voline, Italy [F. B.]; and Istituto di Biometria e Statistica Medica, Università di Milano, Via Venezian 1, 20133 Milano, Italy [C. L. V.]

Abstract

Using data from a case-control study conducted between 1986 and 1992 in Northern Italy on 367 cases of laryngeal cancers (350 men and 17 women) and 1931 hospital controls (1373 men and 558 women), we estimated the relative risks (RR) and the population attributable risks (AR) for laryngeal cancer in relation to tobacco and alcohol consumption and a diet containing little fresh fruit and vegetables (low beta-carotene intake). In men, the RR and their 95% confidence interval (CI), derived from multiple logistic regression, including terms for center, age, and education, plus, simultaneously, tobacco, alcohol, and beta-carotene) were 3.3 (95% CI, 1.9 to 5.5) for ex- or moderate smokers (<15 cigarettes/day) and 8.8 (95% CI, 5.2 to 14.8) for heavy current smokers compared to never smokers; the RR were 1.5 (95% CI, 1.0 to 2.2) for drinkers of 6 to <8 alcoholic drinks/day and 2.2 (95% CI, 1.6 to 3.0) for drinkers of 8 or more drinks/day compared to teetotallers or moderate drinkers; with respect to carotene intake the RR were 1.4 (95% CI, 1.0 to 2.0) for the intermediate tertile and 1.8 (95% CI, 1.3 to 2.5) for the lowest tertile, as compared to the highest tertile of intake. AR were estimated assuming a multiplicative model: the single factor with the largest AR was smoking, which accounted for about 77% of laryngeal cancers in men; alcohol intake explained about 25% of cases, low beta-carotene intake accounted for about 18% of cases, and together the three factors were responsible for about 86% of laryngeal cancers in men. In women, the RR were significant for current smokers compared to never smokers (RR = 23.9, 95% CI, 5.2 to 110.9) and heavy drinkers (≥4 drinks/day) compared to abstainers and light drinkers (<4 drinks/day) (RR = 4.6, 95% CI, 1.4 to 15.2). The AR were similar to those for men (83% for tobacco, 28% for alcohol, 15% for low beta-carotene intake, and 86% for the combination of the three factors). However, all the estimates in women were unstable because of the small number of cases. Thus, intervention on tobacco, alcohol, and a few simple dietary items could, in principle, reduce laryngeal cancer deaths in Italy from 2500 to about 300 per year.

Introduction

On a worldwide scale, Italy has one of the highest mortality rates for laryngeal cancer in men (1–8). From 1985 to 1989 the overall age-standardized rate (world standard) was 6.0/100,000 males, somewhat lower than the highest one in France (8.7) or Hungary (7.7), but substantially higher than rates in the United States (2.0), England and Wales (1.7), Japan (0.9) or Sweden (0.7) (1–3). This is also the non-sex-related neoplasm in Italy with the largest sex difference, with the overall rate in males being about 20 times that in females (1).

Tobacco and alcohol are the major risk factors for laryngeal cancer (4–27) and appear to interact multiplicatively on the RR[3] (5, 11–14, 16, 17, 21). It is not clear, however, whether these factors explain the large variations in laryngeal cancer rates between populations and sexes. Other risk factors, such as a diet containing little fresh fruit and vegetables (10, 15, 19, 26–28) and, in general, a low socioeconomic level (8, 13, 22) may also have a role. Although the RR for dietary factors are much lower than for tobacco and alcohol (10, 15, 19, 26–28), their AR on a population scale may be elevated, since AR depend not only on the factor examined, but also on the prevalence of exposure in the population.

Tobacco, alcohol, and a diet containing little fresh fruit and vegetables could explain a large proportion of esophageal, oral, and pharyngeal cancers in Italian males and females and largely account for the sex differences in mortality (29, 30). Since laryngeal cancer shares several important risk factors with other cancers of the upper digestive and respiratory sites (29, 30)—although their quantitative impact is probably somewhat different (31)—we used a similar approach to quantify the risk attributable to tobacco, alcohol, and a diet poor in fresh fruits and vegetables for laryngeal cancer among men and women separately in Northern Italy.

Subjects and Methods

The present analysis is based on data collected up to December 1992 from an ongoing case-control study of cancers of the larynx, conducted since 1986 in the greater Milan area and the province of Pordenone, Northern Italy, the general design of which has previously been described (19, 20).

Cases were subjects younger than 80 years of age with histologically confirmed incident cancer of the larynx (ICD IX 161), diagnosed within 1 year, admitted to the cancer

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[2] To whom requests for reprints should be addressed.

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

Table 1 Distribution of 367 cases of laryngeal cancer and 1931 controls according to age, education, and center. Milan and Pordenone, Italy, 1986–1992

	Men				Women			
	Laryngeal cancer		Controls		Laryngeal cancer		Controls	
	No.	%	No.	%	No.	%	No.	%
Age (yr)								
≤44	15	4.3	125	9.1	1	5.9	93	16.6
45–54	62	17.7	354	25.8	3	17.6	116	20.8
55–64	180	51.4	560	40.8	6	35.3	179	32.1
65–74	93	26.6	334	24.3	7	41.2	170	30.5
Education (yr)[a]								
<7	254	72.8	793	58.0	10	58.8	356	64.0
7–11	58	16.6	371	27.1	5	29.4	124	22.3
≥12	37	10.6	204	14.9	2	11.8	76	13.7
Center								
Milan	231	66.0	771	56.2	11	64.7	377	67.6
Pordenone	119	34.0	602	43.8	6	35.3	181	32.4

[a] The sum does not add up to the total because of some missing values.

Table 2 Distribution of laryngeal cancer cases and controls and RR estimates with their 95% CI, according to smoking status, total alcohol intake, and estimated beta-carotene intake in men. Milan and Pordenone, Italy, 1986–1992

	Laryngeal cancer	Controls	Relative risk (95% CI)	
			A[a]	B[b]
Smoking status[c]				
Never smokers	17	316	1[d]	1[d]
Moderate smokers[e]	137	683	3.5 (2.1–6.0)	3.3 (1.9–5.5)
Heavy smokers	196	372	10.4 (6.2–17.5)	8.8 (5.2–14.8)
χ^2, trend			135.4 ($P < 0.001$)	108.0 ($P < 0.001$)
Total alcohol intake (drinks/day)[c,f]				
<6	163	855	1[d]	1[d]
6 to <8	47	166	1.6 (1.1–2.3)	1.5 (1.0–2.2)
≥8	136	348	2.7 (2.0–3.6)	2.2 (1.6–3.0)
χ^2, trend			42.4 ($P < 0.001$)	25.2 ($P < 0.001$)
Beta-carotene index (international units/month)[c]				
≥170	72	492	1[d]	1[d]
110 to <170	115	463	1.6 (1.2–2.2)	1.4 (1.0–2.0)
<110	163	417	2.4 (1.7–3.3)	1.8 (1.3–2.5)
χ^2, trend			30.2 ($P < 0.001$)	10.8 ($P = 0.001$)

[a] Estimates from multiple logistic regression, including terms for center, age, and education.
[b] Estimates from a multiple logistic regression model, including terms for center, age, education, and the main effects of the three factors considered, and assuming a multiplicative effect.
[c] The sum does not add up to total because of the missing values.
[d] Reference category.
[e] The moderate smokers category included ex-smokers (RR, 3.9; 95% CI, 2.3 to 6.6), pipe and/or cigar smokers (RR, 2.0; 95% CI, 0.2 to 16.9) and current smokers of <15 cigarettes per day (RR, 2.9; 95% CI, 1.6 to 5.4), adjusted for age, center, and education.
[f] Using as reference category <3 drinks/day the RR was 0.8 (95% CI, 0.5 to 1.1) for 3 to <6 drinks/day. 1.4 (95% CI, 0.9 to 2.1) for 6 to <8 drinks/day and, 2.3 (95% CI, 1.7 to 3.3) for ≥8 drinks/day.

institutes and major teaching and general hospitals of the two areas under study. A total of 350 men and 17 women was interviewed. The median age was 61 years (range, 33–79) for men and 61 years (range, 44–71) for women.

Controls were patients admitted to the same network of hospitals where cases were identified for acute, nonneoplastic, nondigestive, or respiratory tract conditions. All admission diagnoses known or potentially related to smoking, alcohol consumption, or long-term dietary modifications were excluded from the control group. This consisted of 1373 men (median age, 58 years; range, 26–79) and 558 women (median age, 59 years; range, 22–79). Eighteen % of the controls were admitted for traumatic conditions, 25% for nontraumatic orthopedic disorders (mostly low back pain and disc disorders), 41% for acute surgical conditions (such as acute appendicitis or strangulated hernia), and 16% for miscellaneous illnesses (such as ear, eye, dental, or skin disorders).

A structured questionnaire was used by trained interviewers to collect data on socio-demographic characteristics, smoking habits, alcohol consumption, weekly intake of a few selected indicator foods (meat, ham, liver, fish, milk, cheese, eggs, carrots, vegetables, fruit, butter, margarine, oil), including major sources of beta-carotene in the Italian diet (carrots, vegetables, fruit), history of selected conditions and, for women, menstrual and reproductive history. Infor-

mation on smoking included the forms of smoking, the amount smoked per day, age at starting, duration in years and, for ex-smokers, the time since stopping. Smokers were defined as individuals who had smoked at least one cigarette per day for a continuous period of 1 year or more. Ex-smokers were defined as those who had stopped smoking at least 1 year before diagnosis. Information on alcohol included the number of drinks per day for each type of alcoholic beverage (wine, beer, spirits) consumed, the number of days per week, and the duration of the habit in years. As an indicator of total alcohol consumption, the average number of all alcoholic drinks per day was computed (one drink being approximately 150 ml of wine, or 330 ml of beer, or 30 ml of spirits, corresponding to 12–15 g of ethanol).

Using tables of nutrient values issued by the Italian Department of Agriculture (32), we computed an index of beta-carotene intake (in international units/month). Since we collected data only on a limited number of foods in the absence of information on portion size, this index must be taken merely as a weighted indicator of the content in fresh fruit and vegetables in the diet. Even in the absence of any etiological inference, the association with this index was stronger than for each of its component.

Unconditional logistic regression models were used to obtain estimates of the relative risks of laryngeal cancer (33), including terms for age (quinquennia), area of residence (Milan/Pordenone), education (three levels), smoking (three levels) (in men: never smokers/moderate smokers/heavy smokers, moderate smokers including current smokers of <15 cigarettes per day, pipe-cigar and ex-smokers, and heavy smokers including current smokers of ≥15 cigarettes; in women: never smokers/current smokers/ex-smokers), average number of alcoholic beverages per day (in men, <6/6 to <8/≥8; in women, <4/≥4) and a measure of beta-carotene intake (in men: ≥170/110 to <170/<110 international units per month, approximate tertiles; in women: <158/≥158, approximate median). For men, ex-smokers, pipe/cigar smokers and current smokers of <15 cigarettes/day were combined, since their RR were comparable. For alcohol intake, teetotallers and alcohol drinkers of <6 drinks/day were combined, since the RR was not significantly elevated up to this intake. For women, categories were wider because of the small number of cases. The logistic model assumes a multiplicative effect of the terms included in the model. To verify this assumption, models with and without interaction terms were fitted. The difference of the deviances of these models, compared to the χ^2 distribution with number of degrees of freedom (df) equal to the number of extra parameters fitted (33), was not significant. Thus, in the absence of any significant deviation from a multiplicative model, the RR for combined exposures were computed by multiplying the estimated risk for the main effects. Using the distribution of the risk factors in the cases and the RR estimates (33), population attributable risks (AR) were computed, *i.e.*, the proportion of laryngeal cancer cases that would have been avoided if the given exposure(s) had not been present in the population. The method described by Bruzzi *et al.* (34) implies knowledge of the RR estimates and of the joint distribution of the risk factors in the population of cases only and thus can be used for hospital-based case-control studies.

Results

Table 1 presents the distribution of cases and controls according to age, education, and center in both sexes. Among more educated individuals risk was lower for men (about 73% of the cases had fewer than 7 years of education, compared to about 59% of controls), but not for women.

Table 3 Distribution of cases of laryngeal cancer and estimated relative risks for various combinations of consumption of alcohol, tobacco, and beta-carotene in men. Milan and Pordenone, Italy, 1986–1992

Risk level[a] for			No. of cases:controls[b]	Relative risk[c]
Tobacco	Alcohol	Beta-carotene		
–	–	–	4:62	1[d]
+	–	–	24:105	3.3
++	–	–	48:90	8.8
–	+	–	1:9	1.5
+	+	–	9:21	4.7
++	+	–	11:25	12.7
–	++	–	1:13	2.2
+	++	–	21:50	7.2
++	++	–	44:40	19.2
–	–	+	5:68	1.4
+	–	+	24:146	4.6
++	–	+	29:77	12.2
–	+	+	0:15	2.0
+	+	+	10:31	6.6
++	+	+	11:12	17.6
–	++	+	0:12	3.0
+	++	+	17:60	10.0
++	++	+	19:40	26.6
–	–	++	3:96	1.8
+	–	++	16:154	5.7
++	–	++	15:54	15.3
–	+	++	1:16	2.5
+	+	++	2:29	8.3
++	+	++	1:8	22.2
–	++	++	2:23	3.8
+	++	++	13:84	12.5
++	++	++	19:26	33.5

[a] –, the lowest risk; +, the medium risk; ++, the highest risk category.
[b] The sum does not add up to the total because of some missing values.
[c] Estimates from a multiple logistic regression model, including terms for center, age, education, and the main effects of the three factors considered, and assuming a multiplicative effect.
[d] Reference category.

The relationship between the risk of cancer of the larynx and smoking, alcohol drinking, and beta-carotene intake in men is presented in Table 2. Compared to never smokers, the multivariate RR were 3.3 for the combination of ex, pipe/cigar and current moderate smokers (<15 cigarettes/day), and 8.8 for heavy smokers (≥15 cigarettes/day); the trend in risk was highly significant ($P < 0.001$). With reference to alcohol drinking, there was no evidence of increased risk up to 6 drinks/day. Compared to drinkers of fewer than 6 alcoholic drinks/day, men drinking 6 to <8 drinks/day had a multivariate RR of 1.5, while those who drank 8 or more drinks/day had a RR of 2.2; the trend in risk was significant ($P < 0.001$). A low intake of beta-carotene in men was associated with a significantly higher risk of cancer, the multivariate RR being, respectively, 1.4 and 1.8 for the intermediate and lowest tertiles of intake compared to the highest one, and the trend in risk was also significant ($P = 0.001$).

Table 3 shows the distribution of cases of laryngeal cancer according to all possible combinations of tobacco, alcohol, and beta-carotene intake and the RR estimates in men. Only 4 men (0.1%) were in the lowest risk category (reference = 1), and 19 (5.4%) were in the highest one. The risk of laryngeal cancer for the highest levels of smoking was 8.8 and increased nearly 20-fold for heavy smokers and alcohol drinkers relative to the lowest levels of both factors (RR = 19.2) and more than 30-fold when the

Table 4 Distribution of laryngeal cancer cases and controls and relative risk estimates with their 95% CI, according to smoking status, average total alcoholic beverage and beta-carotene intake in women. Milan and Pordenone, Italy, 1986–1992

	Laryngeal cancer	Controls	Relative risk (95% CI)	
			A[a]	B[b]
Smoking status				
Never smokers	2	400	1[c]	1[c]
Ex-smokers	1	52	3.9	3.7
Current smokers	14	106	32.5 (7.4–142.0)	23.9 (5.2–110.9)
Total alcohol intake (drinks/day)[d]				
<4	11	520	1[c]	1[c]
≥4	6	37	8.7 (3.0–25.4)	4.6 (1.4–15.2)
Beta-carotene index (international units/month)[d]				
≥158	5	281	1[c]	1[c]
<158	12	276	2.9 (0.9–8.8)	2.0 (0.6–7.2)

[a] Estimates from multiple logistic regression, including terms for center, age, and education.
[b] Estimates from a multiple logistic regression model, including terms for center, age, education, and the three factors considered.
[c] Reference category.
[d] The sum does not add up to the total because of some missing values.

lowest intake of beta-carotene was associated (RR = 33.5). Among women (Table 4) current smokers and heavy drinkers (≥4 drinks/day) had a substantially increased risk (multivariate RR, respectively, 23.9 and 4.6), while the RR for a low intake of beta-carotene was 2.0. All the estimates in women, however, must be considered with extreme caution because of the small number of cases.

AR derived from the multiplicative model are presented in Table 5. In men the single exposure with the highest AR was smoking, which accounted for approximately 77% of laryngeal cancer cases. Alcohol, as a single factor, explained about 25% of cases and low beta-carotene explained 18% of cases. Together, the three factors were responsible for approximately 86% of laryngeal cancers. AR in women were very similar (about 83% for smoking, 28% for alcohol intake, 15% for a low beta-carotene intake, and 86% for the three factors together), although they were subject to much wider random variation on account of the few cases on which computation was made.

Table 5 Attributable risk percentages of laryngeal cancer in relation to selected risk factors and their combination. Milan and Pordenone, Italy, 1986–1992

Factor	Attributable risk percentage[a]	
	Men	Women[b]
Smoking	76.8	83.2
Alcohol	25.3	27.7
Beta-carotene	18.0	15.0
Smoking + alcohol	82.2	84.4
Smoking + beta-carotene	81.4	84.5
Alcohol + beta-carotene	38.8	42.7
Smoking + alcohol + beta-carotene	85.7	85.7

[a] Estimates from a multiple logistic regression model including terms for center, age, education, and the main effects of the three factors considered, and assuming a multiplicative effect.
[b] Estimates in women were based on a very small number and hence subject to substantial variation.

Discussion

This study confirms that smoking, heavy alcohol drinking, and low consumption of fresh fruit and vegetables are risk factors for cancers of the larynx and indicates that about 86% of cancers among men in Northern Italy can be attributed to the combination of these risk factors. The most important single exposure was smoking, which alone could explain about 77% of cases. Despite the much smaller number of cases, the AR for women were comparable to those in men. There is evidence that tobacco and alcohol (4–27) are important risk factors for laryngeal cancer and that they are the major causes of laryngeal cancer in several populations. Zatonski *et al.* (21) reported AR for smoking alone of 95% in Polish men and Burch AR of 94% for the association of tobacco and alcohol in a Canadian study (9). In several populations, therefore, the majority of laryngeal cancers can be attributed to recognized risk factors.

Our figures may be somewhat underestimated, since there are several limits and approximations on available data. Our beta-carotene index should be viewed only as an indicator of the intake of fruit and vegetables or of a well balanced diet, given the small number of food items for which information was available and the persistent uncertainty on which component(s) of a diet rich in foods of plant origin affords protection. Relatively broad categories were used for tobacco and alcohol consumption and this may have caused some underestimation of AR. Thus, the overall AR is probably somewhat higher than the estimates given.

Another potential limitation of this study is the use of hospital controls in the investigation of tobacco and dietary habits (35, 36). However, all admission diseases which were known or suspected to be related to tobacco, alcohol consumption, and long-term modifications of diet were carefully excluded and the hospital setting may make recall more comparable for cases and controls (35, 36). The interviews were conducted in the same setting for cases and controls, participation was almost complete (less than 3% of cases and controls refused interview), cases and controls were drawn from the same catchment areas, and allowance for several confounding factors did not notably modify the relative risk estimates in men. Thus it is unlikely that the present results were largely influenced by information, selection, or confounding bias.

In the computation of the AR, it was assumed that cases were representative of the population of cases in the regions under study. These areas have no cancer registries, so the

exact proportion of cases identified and questioned is not known. However, our study covered the main hospitals in the two areas, and there is no reason to assume any major systematic selection mechanism.

The sum of the three factors considered gives an AR of 120% in males and 125% in females, which is therefore greater than the combination of the three factors. This is not surprising, since under a multiplicative model, whenever risk factors are not mutually exclusive, a neoplasm associated with two different factors is singularly attributed to both and so the combined AR will differ from the sum of AR for each factor. This difference is larger when the AR for each factor are greater.

In previous articles, based on similar datasets and methods, we estimated that over 90% of cases of esophageal cancer (29) and over 85% of cases of oral cancer (30) in Northern Italy could be attributed to tobacco, alcohol, and a diet containing little fresh fruit and vegetables. For cancer of the larynx the estimated AR was 86%. Intervention on tobacco, alcohol, and simple dietary items could thus in principle reduce the number of deaths from this type of cancer in Italy from over 2,500 to about 300 per year. In the absence of exposure to these well identified risk factors, laryngeal cancer would thus become extremely rare.

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