
RESEARCH COMMUNICATION

Assessment of Risk Factors in Laryngeal Cancer in India : A Case- Control Study

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Abstract

Cancer of the larynx is fourteenth most common cancer in the world. Limited data are available from India on associations with risk factors and hence the present hospital based matched case-control study was conducted. Three hundred and five laryngeal cancer patients and an equal number of healthy controls matched for their age within 2 years, sex and place of residence constituted the study population. A pre-tested, semi-structured questionnaire was administered to each individual to elicit information on their socio-demographic profile, food habits and risk factors and dietary consumption patterns. Univariate logistic regression analysis and multivariate forward stepwise conditional logistic analysis were performed. In the univariate analysis a lower consumption of roots and tubers green leaf vegetable other vegetables and fruits, and higher consumption of milk, eggs, meat, tea, alcohol, smoking, consumption of betel leaf with tobacco as well as a preference for spicy and fried foods emerged as significant positive variables. After adjusting for education, years of use of alcohol, smoking, chewing of betel leaf with tobacco in the model, low green leafy vegetables and preference for spicy foods were found to be positively related to the risk of laryngeal cancer. There was a significant difference in the dietary consumption patterns of laryngeal cancer patients and controls, indicating a role for nutritional factors in the etiology of laryngeal cancer in the Indian population.

Key Words: Laryngeal cancer - case-control study - risk factors - diet - nutrition

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Introduction

Cancer continues to be a major health problem despite advances in medical technology for its diagnosis and treatment. Cancer of the larynx is fourteenth most common cancer in the world. In 1996, an estimated 190,000 new cases of laryngeal cancer were diagnosed worldwide, accounting for 1.8 percent of all new cancers (WHO, 1997). Sixty percent of the global incidence of laryngeal cancer is found in developing countries. In India, the incidence of laryngeal cancer has been reported to be 1.3 to 8.8 per 1,00,000 population, in six different regions in the country (ICMR, 1992). Several epidemiological studies suggest that smoking and chewing of tobacco are risk factors for cancer and diets high in vegetables and fruits, together with consumption of little if any alcohol, may prevent between 33 percent and 50 percent of all cases of laryngeal cancer (WHO, 1997; Steinmetz and Potter, 1991). Data on the nutritional factors associated with cancer of larynx are limited mainly to certain parts of the globe. Limited data

are available from India on the association of risk factors with carcinoma larynx and hence the present case-control study was undertaken.

Methodology

The study was a hospital based case-control study consisting of 305 laryngeal cancer patients and an equal number of matched controls. The study was conducted during 2000 to 2002.

Review of literature suggest that, there are no studies which provide complete information regarding risk factors of laryngeal cancer, that is, relative risk (estimated by odds ratio) for laryngeal cancer regarding various exposure-variables and prevalence of exposure-variables among cases and controls. A study conducted in India reported only odds ratio considering 80 laryngeal cancer cases and 215 hospital based controls (Notani and Jayant, 1987). Therefore, to work-out sample size for present study, these results have been used. Accordingly, the required minimum

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sample size at 95% level of confidence, 80% power of the study and for two sided test, for majority of the variables, ranged between 25 to 300. Hence, it was decided to include at least 300 laryngeal cancer patients and an equal number of matched controls in the study to ensure higher precision in the results.

Three hundred and five diagnosed laryngeal cancer patients (all consecutive cases) from the out-patient and hospital admissions of the Department of Otorhinolaryngology and head and neck tumor clinic at the Institute Rotary Cancer Hospital, constituted the study population. The criteria for the selection of patients were i) proven cases of laryngeal cancer by biopsy and histopathology; ii) who had not undergone any treatment ie. chemotherapy or radiotherapy; iii) who were in good mental health to give reliable answers to the questionnaire; iv) who did not suffer from any major illness in the past, before the diagnosis of laryngeal cancer so as to change their dietary consumption pattern; v) who had not taken long course of any vitamin or mineral supplement during the last one year and vi) who were not on corticosteroid therapy or were not suffering from hepatic disorders or severe malnutrition.

Three hundred and twenty normal healthy individuals accompanying the patients in the department of Gastroenterology, Medicine and Surgery at the hospital constituted the control group. The criteria for the selection of controls was i) who were not related to the patients included in the study ii) who were not suffering from any cancerous lesions iii) who were in good mental health to give reliable answers to the questionnaire; iv) who had not taken long course of any vitamin or mineral supplement during the last one year. Individuals in the control group were individually matched with the patients for their age \pm 2 years, sex and place of residence (Rural/Urban). An ethical clearance was obtained from the local review board of the institute and the informed consent of the patients and controls to participate in the study was taken. The period of recruiting cases and controls was 2 years.

The patient and control groups were subjected to similar investigations. A pre-tested, semi-structured questionnaire was administered to each individual to elicit information on socio-demographic profile and socio-economic status was stratified based on the modified Kuppuswamy's classification (Mishra and Singh, 2003). Information was also collected on food habits and other risk factors like history of alcohol consumption, smoking, tobacco chewing and chewing of betel leaf with tobacco. The subjects were also asked whether they had preference for spicy and fried foods. Dietary consumption pattern during the preceding 5 years prior to the diagnosis of the laryngeal cancer was also assessed utilising the standard food frequency questionnaire method (Thimmayamma, 1987).

The descriptive statistics ie. frequency distributions and percentages of demographic profile and various risk covariates have been calculated and presented in Table 1. An exploratory analysis was done to finalise the categorization of some of the variables into appropriate forms

for the study and then subsequently coded. In case there was a category where the number of subjects was very less in comparison to the number of subjects of the other categories, the category with very less number was merged with the immediate next category. The Univariate logistic regression analysis [unadjusted RR (OR)] has been performed to see the significance level of each variable (Table 2, 3 and 4). Variables age, sex and place of residence have been matched in case and controls. The probable covariates to be considered in the multivariate analysis were finalized through both statistical and theoretical approach. Hence, a Multivariate forward stepwise conditional logistic analysis taking inclusion and exclusion criteria of 0.10 and 0.05, respectively has been performed. Risk factors after adjusting education, years of use of alcohol, smoking and tobacco chewing covariates have been presented in Table 5. The result was considered significant at 5% level of significance. The BMDP 7.0 statistical software package has been used for the analysis

Results

The distribution of laryngeal cancer patients and controls according to their socio-demographic profile is depicted in Table 1. Nearly 89.8 percent of the patients were in the age group of 41-80 years. The prevalence of laryngeal cancer was higher in males than females with a male: female ratio of 11.2 : 1. Majority of the patients (54.1 percent) belonged to urban area. It was found that 81.7 percent of the patients belonged to lower middle and upper lower socio-economic

Table 1. Distribution of Laryngeal Cancer Patients and Controls According to Their Socio-demographic Profiles

Socio-demographic particulars	Laryngeal cancer patients	Controls
Age (years)		
<40	27 (8.9)	27 (8.9)
41-45	21 (6.9)	19 (6.2)
46-50	40 (13.1)	37 (12.1)
51-55	55 (18.0)	61 (20.0)
56-60	45 (14.8)	42 (13.8)
61-65	54 (17.7)	57 (18.7)
66-70	29 (9.5)	20 (6.6)
71-75	25 (8.2)	32 (10.5)
76-80	5 (1.6)	6 (2.0)
>81	4 (1.3)	4 (1.3)
Sex		
Males	280 (91.8)	280 (91.8)
Females	25 (8.2)	25 (8.2)
Place of residence		
Urban	140 (45.9)	140 (45.9)
Rural	165 (54.1)	165 (54.1)
Socio-economic status		
Upper	5 (1.6)	14 (4.6)
Upper middle	27 (8.9)	56 (18.4)
Upper Lower	214 (70.2)	161 (52.8)
Lower Middle	35 (11.5)	69 (22.6)
Lower	224 (7.9)	5 (1.6)

Figures in parenthesis denote percentages

Table 2. Unadjusted Relative Risk of Laryngeal Cancer According to Alcohol Consumption, Smoking and Chewing of Betel Leaf with Tobacco

Dietary variables Patients	Laryngeal cancer	Controls	Odds ratio	95 % CI
Alcohol consumption				
No	175(57.4)	257(84.3)	1.00	
Yes	130(42.6)	48(15.7)	3.98	2.66, 5.94
Smoking				
No	69(22.6)	174(57.0)	1.00	
Yes	236(77.4)	131(43.0)	4.54	3.15, 6.56
Tobacco chewing				
No	264(86.6)	267(87.4)	1.00	
Yes	41(13.4)	38(12.5)	1.09	0.66, 1.79
Chewing of betel leaf with tobacco				
No	278(91.1)	293(96.1)	1.00	
Yes	27(8.9)	12(3.9)	2.37	1.12, 5.06

Figures in parenthesis denote percentages

status as per the Kuppaswamy's classification.

There was a strong positive association between the relative risk of laryngeal cancer and alcohol consumption, smoking and chewing of betel leaf with tobacco. The relative risk increased from the reference value of 1.0 with no alcohol consumption to 3.98 with consumption of alcohol. Smoking and chewing of betel leaf with tobacco were found to increase the risk for laryngeal cancer 4.54 and 2.37 fold, respectively. No significant difference was observed between laryngeal cancer and tobacco chewing (Table 2).

It was found that 99.2 percent of the patients and controls consumed wheat as their staple diet, whereas 49.6 and 38.1 percent patients and controls, respectively, consumed both rice and wheat.

The results revealed that roots and tubers were consumed three times to once per week by 26.2 percent of the patients and 6.2 percent of the controls, respectively (Table 3). The risk of laryngeal cancer was 5.25 times higher for those who consumed roots and tubers less than four times per week. There was also an inverse association between the risk of

laryngeal cancer and consumption of other vegetables and green leafy vegetables. The relative risk of laryngeal cancer increased to 2.20 and 5.67 times for those who consumed other vegetables and green leafy vegetables less than four times per week, respectively. Consumption of fruits less than four times and once per week increased the relative risk of laryngeal cancer 3.28 and 4.78 times, respectively (Table 3).

Milk was consumed daily to four times per week by 47.5 percent of the laryngeal cancer patients and 74.4 percent of the controls, respectively. The relative risk was 0.24 times for those who consumed milk less than four times per week and it increased to 0.45 for those who consumed less than once per week (Table 4).

Nearly 48.5 percent and 49.9 percent of the patients and 25.9 percent and 32.1 percent of the controls consumed eggs and flesh foods, respectively. There was a nearly three and two fold increase in risk of laryngeal cancer with consumption of eggs and Hesh foods, respectively (Table 4). The relative risk for laryngeal cancer increased 4.20

Table 3. Unadjusted Relative Risk of Laryngeal Cancer According to Dietary Variables

Dietary variables	Laryngeal cancer Patients	Controls	Odds ratio	95% CI
Roots and Tubers				
Daily - 4/week	225(73.8)	281(92.1)	1.00	
3/week – 1/week	80(26.2)	19(6.2)	5.25	3.01, 9.27
Occasional/ do not take	0(0.0)	5(1.7)		
Other vegetables				
Daily - 4/week	80(26.2)	133(43.6)	1.00	
3/week – 1/week	225(73.8)	170(55.7)	2.20	1.54, 3.14
Occasional/ do not take	0(0.0)	2(0.7)		
Green leafy vegetables				
Daily - 4/week	48(15.7)	158(51.8)	1.00	
3/week – 1/week	241(79.0)	140(45.9)	5.67	3.79, 8.48
Occasional/ do not take	16(5.3)	7(2.3)	7.52	2.71, 21.60
Fruits				
Daily –4/week	38(12.5)	103(33.8)	1.00	
3/week – 1/week	195(63.9)	161(52.8)	3.28	2.09, 5.14
Occasional/ do not take	72(23.6)	41(13.4)	4.75	2.69, 8.43

Figures in parenthesis denote percentages

Table 4. Unadjusted Relative Risk of Laryngeal Cancer According to The Dietary Variables

Dietary variables	Laryngeal cancer Patients	Controls	Odds ratio	95% CI
Milk				
Daily –4/week	145(47.5)	227(74.4)	1.00	
3/week – 1/week	97(31.8)	33(10.8)	0.24	0.13,0.44
Occasional/ do not take	63(20.7)	45(14.8)	0.45	0.28,0.72
Eggs				
Do not take	157(51.5)	226(74.1)	1.00	
Take	148(48.5)	79(25.9)	2.69	1.89,3.85
Meat				
Do not take	153(50.0)	207(67.9)	1.00	
Take	152(49.9)	98(32.1)	2.09	1.49,2.95
Tea				
Do not take	8(2.6)	31(10.2)	1.00	
Take	297(97.4)	274(89.8)	4.20	1.8,10.09
Spicy food				
No	152(49.8)	213(69.8)	1.00	
Yes	153(50.2)	92(30.2)	2.33	1.65,3.29
Fried food				
No	128(42.0)	159(52.1)	1.00	
Yes	177(58.0)	146(47.9)	1.50	1.08,2.10

Figures in parenthesis denote percentages

times with consumption of tea. There was a statistically significant difference between the patients and controls with respect to the preference for spicy and fried foods.

After adjusting for education, years of use of alcohol, smoking, chewing of betel leaf with tobacco, in the model, green leafy vegetables and preference for spicy foods were found to be positively related to the risk of laryngeal cancer. A 3.72 fold increase in risk was observed with consumption of green leafy vegetables less than four times per week and it increased to nearly 5 times with consumption less than once a week. Nearly a two fold increase in risk of laryngeal cancer was observed in those having a preference for spicy foods (Table 5).

Discussion

The mean age of the laryngeal cancer patients was 57 years. These results are consistent with those reported in earlier studies (Maier and Tisch, 1997; Elwood et al., 1984). In the present study, laryngeal cancer was found predominantly in males. It has been reported in earlier studies that laryngeal cancer has the marked male excess as compared to females (ICMR, 1992; Maier and Tisch,

1997; Wynder et al., 1956). In the present study 82 percent of the laryngeal cancer patients belonged to the lower socio-economic status. A low socio- economic status leads to a lower purchasing power and hence the diets consumed are inadequate in terms of quantity and quality which in turn is deficient in nutrients. There is evidence that mineral and vitamin deficiencies are associated with the risk of laryngeal cancer.

The results of the present case- control study revealed that decreased consumption of roots and tubers (less than four times per week) increased the risk for laryngeal cancer 5.25 times. If other vegetables and green leafy vegetables were consumed less than four times per week, the risk for laryngeal cancer was 2.20 and 5.67 times higher, respectively. Consumption of fruits less than four times and once per week increased the relative risk of laryngeal cancer 3.28 and 4.78 times, respectively. Several earlier studies have also shown a protective effect of the intake of fruits and vegetables (Graham et al., 1981; Esteve et al., 1996; La Vecchia et al., 1990; Zheng et al., 1992). An earlier study conducted in India reported the relative risk (RR) for vegetable intake adjusted for the age and tobacco habits as 1.29 and 2.75 for hospital controls and population controls,

Table 5. Adjusted Relative Risk of Laryngeal Cancer for Various Covariates : Results of Stepwise Conditional Logistic Regression

	Laryngeal cancer Patients	Controls	Odds ratio	95% CI
Green leafy vegetables				
Daily – 4/week	48	157	1.00	
3/week – 1/week	241	141	3.72	2.23,6.21
Occasional/never	16	7	4.93	1.52,16.0
Preference of spicy foods				
No	152	213	1.00	
Yes	153	92	1.83	1.15,2.92

respectively. The RR for fruit intake in the two control groups was reported as 1.55 and 2.00, respectively (Notani and Jayant, 1987). Another study conducted in Italy reported the OR as 0.2 (95 percent confidence interval: 0.1, 1.4) for fiber from vegetables, 0.5 (95 percent confidence interval: 0.3, 0.7) from fruits) (Pelucchi et al., 2003). Significant inverse associations were also observed for raw vegetables (OR=0.2), cooked vegetables (OR=0.3) and fruits (OR=0.5) in a case control study conducted in Italy and Switzerland (Bosetti et al., 2002). A case control study was conducted amongst 148 laryngeal cancer cases and 444 frequency matched controls. High consumption of fruits and vegetables was associated with a strong reduction in risk OR 0.42 (95 percent confidence interval: 0.21, 0.84) (De Stefani et al., 2000). Vegetables and fruits are the principal sources of β -carotene, vitamin C and several other micronutrients that prevent the formation of carcinogens from precursor compounds (Watterberg, 1985). Vitamin C and carotenoids are considered to be antioxidants that scavenge and reduce nitrates, thereby reducing the substrate for the reaction with secondary amines to form nitrosamines.

The relative risk was 0.24 times for those who consumed milk less than four times per week and it increased to 0.45 for those who consumed less than once per week. There was a nearly three and two fold increase in risk of laryngeal cancer with consumption of eggs and flesh foods, respectively. An earlier study conducted in India reported a statistically non significant increase in laryngeal cancer with high consumption of eggs (RR=0.97) in hospital controls and (RR=0.64) in population controls (Maier and Tisch, 1997; Notani and Jayant, 1987). There was a statistically significant difference between the patients and controls with respect to the preference for spicy and fried foods.

Alcohol drinking and tobacco smoking are known to be major risk factors for laryngeal cancer (Maier and Tisch, 1997; Elwood et al., 1984). In the present study there was a strong positive association between the relative risk of laryngeal cancer and alcohol consumption, smoking and chewing of betel leaf with tobacco. The relative risk increased from the reference value of 1.0 with no alcohol consumption to 3.98 with consumption of alcohol. Earlier studies have also shown significantly higher alcohol consumption in laryngeal cancer patients as compared to controls (Wynder et al., 1956). In the highest category of alcohol intake (7 oz/day or more), the OR was 5.3 compared to non drinkers. This finding has been confirmed by subsequent studies in Europe (La Vecchia et al., 1990; Spalajkovic, 1976; Brugere et al., 1986; Tuyns et al., 1988; Tavani et al., 1994) and North America (Freudenheim et al., 1992; Hinds et al., 1979; Burch et al., 1981; Hedberg et al., 1994) where a positive dose-response relationship has been observed between alcohol intake and cancer of the larynx. It is hypothesised that alcohol either potentiates other carcinogens, damages the epithelium directly, causes a deficiency of riboflavin, or disturbs the synthesis of immunoglobulin A. Similarly, poor nutrition secondary to the consumption of alcohol could lead to lower levels of

serum albumin and vitamin deficiency (Wynder, 1971; Wynder et al., 1976).

Smoking and chewing of betel leaf with tobacco were found to increase the risk for laryngeal cancer 4.54 and 2.37 fold, respectively. An earlier study conducted in India, reported the relative risk for laryngeal cancer amongst tobacco chewers vs. nonchewers as 1.8 times higher (Notani and Jayant, 1987). Burning the tobacco releases the tar from which, so far, about a dozen polycyclic aromatic hydrocarbons have been isolated, which are known carcinogens. The best known include methylcholanthrene, benzopyrene and benzanthracene. These substances reach the cellular surface of the epithelium in the smoke or dissolved in saliva. Breakdown of these carcinogens by arylhydrocarbon hydroxylase produces the actual carcinogenic epoxides that bind to the DNA and RNA molecules (Hoffman et al., 1976). Tobacco smoke acts as a direct carcinogen - delivery system, with alcohol providing more ready access to cells for tobacco carcinogens via its solvent properties, and more DNA damage in its own right via its first metabolite, acetaldehyde. Both alcohol and tobacco increase the risk likelihood of promotion because of their capacity to damage and kill cells, as a result of oncogene mutation, or loss of tumour suppressor genes (Potter, 1997). The present case-control study revealed significant differences in the dietary consumption patterns of laryngeal cancer patients and controls, indicating the possible role of nutritional factors in the etiology of laryngeal cancer in the Indian population.

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