

Opium and Risk of Laryngeal Cancer

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Objectives/Hypothesis: The study was performed to investigate the possible association between opium dependency and laryngeal cancer. **Study Design:** A hospital-based, group-matched, case-control study was presented. **Methods:** Ninety-eight patients with laryngeal cancer and 312 age- and gender-matched control subjects were selected at the otorhinolaryngology ward of a referral university-affiliated hospital. Data on cigarette smoking and alcohol and opium dependency were collected before surgery through semi-structured interview. **Results:** The crude odds ratios of laryngeal cancer were 15.07 (95% confidence interval [CI], 6.92–32.8 [$P < .0001$]) for cigarette smoking, 21.55 (95% CI, 10.54–44 [$P < .0001$]) for opium dependency, and 1.84 (95% CI, 1.008–3.38 [$P < .048$]) for male gender. Because of strong associations, a logistic regression model was prepared; the odds ratio for gender in the final model was 0.87 (95% CI, 0.39–1.92 [$P = .11$]). According to the results, it seemed that gender was not an independent risk factor for laryngeal cancer. Also, the adjusted odds ratios for smoking (5.21) (95% CI, 2.33–11.67 [$P < .002$]) and opium dependency (10.74) (95% CI, 5.76–20.02 [$P < .002$]) were lower than the crude odds ratios, but both ratios were significant. The mean patient ages were 55.1 years (SD = 12.05 y) in opium-dependent patients and 65.6 years (SD = 12.8 y) in opium-nondependent patients ($P = .01$). **Conclusion:** The results of the study suggest that opium dependency is not only an independent possible risk factor for laryngeal cancer but also significantly increases the likelihood of developing of the disease at a younger age. **Key Words:** Larynx, cancer, opium, dependency, smoking.

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INTRODUCTION

Laryngeal cancer remains the second most common respiratory cancer after lung cancer worldwide, with an increased incidence in many parts of the world, which is generally thought to be related to tobacco and alcohol

consumption.¹ The occurrence of the disease is mostly in the fifth to seventh decades of life, with male-to-female ratios of 15 to 1 since the early 1960s and of approximately 4 to 1 recently.² Laryngeal cancer is two to three times more frequent in individuals who reside in urban and industrial areas than in those who reside in rural areas. The incidence of the disease is significantly higher in male patients of lower socioeconomic status.³

Laryngeal cancer is attributed to tobacco and alcohol consumption with tobacco playing a greater role. Cigarette smoking and the rate of smoking are directly related to the increased risk of cancer. The risk of cancer incidence is lower in pipe smokers or cigar smokers than in cigarette smokers.⁴ It appears that the residual tars, which contain polycyclic aromatic hydrocarbons, are carcinogenic, not nicotine.⁵ In addition, many other factors such as diet, irradiation, papilloma virus infection, and laryngopharyngeal reflux seem to be significant carcinogenic cofactors,⁶ and there are other chemical environmental carcinogenic risk factors such as asbestos,⁷ formaldehyde, and coal dust.⁸ Recently, more attention has been paid to genetic risk factors in laryngeal cancer.⁹

Opium consumption is a major problem in some parts of the world. Opium has been shown to be a risk factor in oral, bladder, and esophageal cancer in southern and northern Iran.^{10–14} The present study was designed to investigate the possible correlation between the cofactor of opium consumption and laryngeal cancer.

PATIENTS AND METHODS

A group-matched, case-control study was performed in a referral Kerman University of Medical Sciences–affiliated hospital in the Kerman province of southern Iran. The study was performed over the 6-year period, from September 1996 to September 2002. In the present study, 98 patients with pathologically confirmed laryngeal squamous cell carcinoma were selected. All gender- and age-matched patients (312 patients in all) who were admitted to the otolaryngology department in the same period were selected as control subjects. Patients with other cancers of the head and neck were excluded because of a possible effect of opium. The data were collected through face-to-face, semi-structured interview before operation. Patients who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Revised*, criteria for opium dependency and opium consumption for at least 5 years were considered as opium dependent. However, types of consumption were not recorded because of multiple routes of ingestion and a possible recall bias. Duration of cigarette smoking and number of cigarettes per day were also recorded.

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Data were analyzed using Stata, version 6, software. Cancer was considered as the outcome of interest and opium dependency as a primary exposure; the confounding effects of gender and smoking were also assessed. The pack-year of smoking was computed by dividing the number of consumed cigarette per day by 20 to obtain the number of packs per day and multiplying that number by the duration of smoking in years. The relationship between cancer and potential risk factors was assessed by classic and logistic regression methods. The 95% confidence interval (CI) of odds ratio (OR) was reported to show the precision of estimation. The significance of each term in the model and also the linear trend of ordinal variable were assessed by "likelihood ratio test." Because of a low number of non-opium-dependent subjects who were non-smokers, it was impossible to access the interaction between these two variables.

RESULTS

The distribution of gender, age, smoking, and opium dependency in patients and control groups is shown in Table I. The minimum and maximum numbers of control subjects per each patient were 2 and 14, respectively. The wide range of numbers of control subjects per case could be explained by the fact that all gender- and age-matched patients were selected as control subjects without any predefined limitation criteria. Because of age matching, there was a significant difference between two groups (gender, $P < .02$; smoking and opium dependency, $P < .0001$), but there was no significant difference in age of patients and control subjects ($z = 0.63$, $P = .52$).

TABLE I.
Distribution of Variables in Cases and Control Subjects.

Characteristic	Controls: No. (%)	Cases No. (%)	(df) Comparison*
Number	312 (76.1)	98 (23.9)	—
Age (y)			
≤45	58 (18.6)	24 (24.5)	
46–55	85 (27.2)	14 (14.3)	$\chi^2 = 8.6$ (3)
56–65	102 (32.7)	31 (31.6)	$P = 0.035$
>65	67 (21.5)	29 (29.6)	
Mean values (SD)	56.7 (10.1)	57.5 (12.9)	$z = 0.63$, $P = 0.52$
Gender			
Female	78 (25)	15 (15.3)	$\chi^2 = 3.99$ † (1)
Male	234 (75)	83 (84.7)	$P = 0.047$
Duration of smoking (y)			
<1	197 (63.1)	10 (10.1)	
1–20	45 (14.4)	27 (27.6)	$\chi^2 = 86.6$ (3)
21–35	26 (8.3)	27 (27.6)	$P < 0.0001$
>35	44 (14.1)	34 (34.7)	
Mean values (SD)	10.2 (14.9)	28.1 (14.4)	$z = 10.4$, $P < 0.0001$
Number of cigarettes per day			
0	197 (63.1)	10 (10.1)	
1–20	37 (11.9)	45 (45.9)	$\chi^2 = 95$ (3)
21–35	47 (15.1)	30 (30.6)	$P < 0.0001$
>35	31 (9.9)	13 (13.4)	
Mean values (SD)	10 (15)	23.8 (11.7)	$z = 8.35$, $P < 0.0001$
Pack-years of smoking			
0	197 (63.1)	10 (10.2)	
1–19	23 (7.4)	4 (4.1)	$\chi^2 = 111.3$ (3)
20–39	29 (9.3)	43 (43.9)	$P < 0.0001$
40–59	32 (10.3)	28 (28.6)	
≥60	31 (9.9)	13 (13.3)	
Mean values (SD)	16.2 (32)	35.1 (30.6)	$z = 5.14$, $P < 0.0001$
Current smoking			
No	197 (63.1)	10 (10.2)	$\chi^2 = 83.6$ † (1)
Yes	115 (36.9)	88 (89.8)	$P < 0.0001$
Current opium dependency			
No	271 (86.9)	23 (23.5)	$\chi^2 = 147.7$ † (1)
Yes	41 (13.1)	75 (76.5)	$P < 0.0001$

* χ^2 test

† χ^2 test with Yates correction (continuity correction).

df, degrees of freedom; z, statistical variable.

The odds ratios for smoking, opium dependency, and gender are shown in Table II. As shown in Table II, these variables are risk factors of laryngeal cancer (gender OR, 1.84 [95% CI, 1.008–3.38; $P < .048$]; smoking OR, 15.07 [95% CI, 6.92–32.8; $P < .0001$]; opium dependency OR, 21.55 [95% CI, 10.54–44, $P < .0001$]).

In the control group, 20.5% of female and 42.3% of male subjects were smokers ($\chi^2 = 11.9$, degrees of freedom [df] = 1, $P < .0001$) and 6.4% of female and 15.4% of male subjects were opium dependent ($\chi^2 = 4.13$, df = 1, $P < .05$). The odds ratios for smoking and opium dependency in the control group and patient group combined were 24.5 (95% CI, 10.4–57.8; $P < .001$) and 104.5 (95% CI, 10.5–1042; $P < .0001$), respectively. Because of this strong association, a logistic regression model was prepared. The results of multivariate analyses are shown in Table III. The OR for gender in the final model was 0.87 (95% CI, 0.39–1.92 [$P = .11$]). According to the results, it seems that gender is not an independent risk factor for laryngeal cancer. Also, the adjusted odds ratios for smoking and opium dependency were lower than the crude OR, but both of them were significant (smoking OR, 5.21 [95% CI,

2.33–11.67; $P < .002$]; opium dependency OR, 10.74 [95% CI, 5.76–20.02; $P < .002$]). Because of this strong association between smoking and opium dependency and substantial colinearity, the CI of adjusted odds ratios was wide and it was impossible to explore the effect modification of these variables. Among patients, the mean numbers of cigarettes were 21.9 and 32.9 per day in opium-dependent and opium-nondependent individuals, respectively ($P = .001$), and opium-dependent patients were younger than opium-nondependent ones (55.1 vs. 65.5 y, respectively [$P = .01$]).

DISCUSSION

The absolute etiology of cancer remains unknown, but various risk factors have been reported to be important in induction of cancers. Prevention is more important than treatment, so investigators have been focused on identifying the risk factors of cancer. The most important factors in laryngeal cancer are reported to be smoking and alcohol consumption. The present study was designed to evaluate the impact of opium dependency and smoking in laryngeal cancer.

Cigarette smoking is considered to be the most important known risk factor for laryngeal cancer.³ In a study performed by Sokic et al.¹⁵ in Belgrade, the OR for smoking for more than 10 years was 7.29, and in another study performed by Guo et al.¹⁶ in China, the OR for smoking for more than 10 years was 16.8. In the current study, crude OR was 15.07 (95% CI, 6.92–32.81 [$P = .0001$]) for cigarette smoking (Table II). According to the results, the risk of cancer was not related to the number of cigarettes. Although random error should be taken into account, the lower number of smoked cigarettes per day in opium dependent patients (21.9) in comparison to nondependent group (32.9) might be explained by this finding. On multivariate analysis, the OR smoking decreased by 5.21 (95% CI, 2.33–11.67 [$P < .002$]). Thus, cigarette smoking is an important risk factor.

Although alcohol consumption has been considered an important and independent risk factor for laryngeal cancer, because of social behaviors (mainly, religious restrictions), none of the patients were regular alcohol consumers. Therefore, the role of alcohol consumption as a risk factor could not be considered in the society being studied.

The male-to-female ratio was 15 to 1 since the early 1960s, but recently it has been reported to be approximately 4 to 1.² In the present study, the male-to-female ratio was 7 to 1. Crude OR for male gender was 1.84 (95% CI, 1.008–3.38; $P < .048$); after adjustment estimation by logistic regression there was no significant OR (0.87) (95% CI, 0.39–1.92; $P = .11$). Thus, it seems that gender by itself is not an independent factor. The higher incidence of laryngeal cancer in male patients is probably due to greater consumption of cigarettes and opium in men than in women in the society being studied.

Although numerous studies have been conducted to explore the effect of drug abuse on malignancy, there have been no reports on the effect of dependency, including dependency on LSD, opiates (diacetylmorphine, morphine, opium, and codeine), cocaine, cannabis, and betel

TABLE II.

Result of Crude Odds Ratio of Gender, Smoking, and Opium Dependency With Laryngeal Cancer.

Laryngeal Cancer	Negative (n = 312)	Positive (n = 98)	Crude odds ratio (95% CI)
Gender (%)			
Female	15.3	25	1
Male	84.7	73	1.84 (1.008–3.38)
Duration of smoking (y)			
0	63.14	10.2	1
1–20	14.42	27.55	11.8 (5.34–26.16)
21–35	13.46	33.67	15.48 (7.1–33.9)
>35	8.97	28.57	19.7 (8.6–44.9)
Linear trend	—	—	2.49 (1.99–3.12)
Number of cigarettes per day			
0	63.14	10.2	1
1–20	11.86	45.92	23.9 (9.3–61.5)
21–35	15.06	30.61	12.6 (5.2–30.1)
>35	9.94	13.27	8.3 (3.16–21.6)
Linear trend	—	—	1.96 (1.58–2.43)
Pack-years of smoking			
0	63.14	10.2	1
1–19	7.37	4.08	3.4 (0.98–11.9)
20–39	9.29	43.88	29.2 (10.7–79.6)
40–59	10.26	28.57	17.24 (6.7–44.1)
≥60	9.94	13.27	8.29 (3.16–21.6)
Linear trend	—	—	1.86 (1.59–2.17)
Current smoking			
No	36.86	89.8	1
Yes	63.14	10.2	15.07 (6.92–32.8)
Current opium dependency			
No	13.14	76.53	1
Yes	86.86	23.47	21.55 (10.54–44)

TABLE III.
Crude and Multivariate Adjusted Odds Ratio (OR) for Laryngeal Cancer With Other Potential Risk Factors.

Variable	Crude OR*		Multivariate adjusted OR		P Value
	OR	95% CI	OR	95% CI	
Gender					
Female	1	—	—	—	
Male	1.84	1.008–3.38	0.87	0.39–1.92	.11*
Opium dependency					
No	1	—	1	—	
Yes	21.55	10.54–44	10.74	5.76–20.02	.002*
Smoking					
No	1	—	1	—	
Yes	15.07	6.92–32.8	5.21	2.33–11.67	.002*

*The P-value of likelihood ratio test, which shows the significance of each term in the conditional logistic regression model.

quid, on laryngeal cancer. Li and Lin¹⁷ showed that genotoxicity and carcinogenicity of abused drugs could also be detrimental in Chinese health. Opium dependency is a major social problem in Iran. Exposure to residues from opium pipes is the suspected etiological agent of esophageal cancer in northern Iran.¹⁴ Evidence has been presented that opium dependency is a risk factor for bladder cancer^{11–13} and oral cancer in southern Iran.¹⁰ There has been no report on opium dependency and laryngeal cancer in the literature. In the present study, crude OR for opium consumption was 21.55 (95% CI, 10.54–44; $P < .0001$), which was equal to 10.74 (95% CI, 5.76–20.02; $P < .002$) after adjustment for smoking (Table III). The OR was approximately two times greater than the OR for cigarette smoking, which reveals a stronger relation between opium dependency and laryngeal cancer as compared with cigarette smoking. The age of onset or manifestation of laryngeal cancer is in the fifth to seventh decades of life. In a recent study performed by Albright et al.,² the mean age was approximately 63 years. In the present study, mean age at cancer presentation was 55.1 years (SD = 12.05 y) for opium-dependent patients and 65.5 years (SD = 12.8 y) for the opium-nondependent group, which was significant ($P = .01$). Therefore, the age incidence of laryngeal cancer was 10.4 years lower in opium-dependent patients than in opium-nondependent ones. Laryngeal cancer in individuals under 40 years of age is not frequent and includes less than 2% of all cases.² The roles of known risk factors such as cigarette smoking and alcohol consumption are not clear in patients under 40 years of age, although there were only four opium-dependent patients younger than 40 years of age (6.5%), but all opium-nondependent patients were older than 40 years of age. Therefore, opium dependency might be a risk factor for laryngeal cancer, particularly in patients younger than 40 years of age in the population under survey.

It seems that long-term opium consumption not only has a strong relation to laryngeal cancer but also reduces the age of onset of the disease. The exact mechanisms of opium oncogenicity are not well known. Malaveille et al.¹⁸ discussed the carcinogenicity of opium as a pro-mutagens, producing mostly frame shift mutations in *Salmonella*

typhimurium strains TA1538 and TA98 after metabolic activation.

CONCLUSION

Opium consumption is a possible risk factor for laryngeal cancer, and it significantly reduces the age of onset of the disease.

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