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Opium Could Be Considered an Independent Risk Factor for Lung Cancer: A Case-Control Study

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Key Words
Lung cancer · Opium · Risk factor

Abstract
Background: Lung cancer is the leading cause of cancer-related death worldwide, and half of all incident lung cancers are believed to occur in the developing countries, including Iran. ***Objective:*** We investigated the association of opium with the risk of lung cancer in a case-control study. ***Methods:*** We enrolled 242 cases and 484 matched controls in this study. A questionnaire was developed, containing questions on basic demographic characteristics, as well as lifelong history of smoking cigarettes, exposure to passive smoking, opium use and alcohol consumption. For smoking cigarettes and opium and also oral opium intake frequency, duration and cumulative use were categorized into three groups: no use, low use and high use. Conditional logistic regression was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). ***Results:*** Multivariate analysis in men showed that after adjusting for the effect of ethnicity, education and pack years of smoking cigarettes, smoking opium remained as a significant independent risk factor with an OR of 3.1 (95% CI 1.2–8.1). In addition, concomitant heavy smoking of cigarettes and opium dramatically increased the risk of lung cancer to an OR of 35.0 (95% CI 11.4–107.9). ***Conclusion:*** This study demonstrated that smoking opium is associated with a high risk of lung cancer as an independent risk factor.

Introduction

Lung cancer has been the most common cancer worldwide [1]. It is estimated that 1.35 million cases that lead to 1.2 million deaths (mortality-to-incidence rate ratio is 0.85) occur each year [2]. Lung cancer is more incident in men than women [3]. Half of all incident lung cancers are believed to occur in the developing countries, including Iran [2]. The incidence of lung cancer in Iran has been

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reported to be from 4.7 to 9.2 and 1.5 to 4.6 cases per 100,000 in men and women, respectively [2, 4]. In Iran, lung cancer is one of the five major cancers. Its rate has been increasing in both men and women over the past decades, with an overall estimated 5-year survival rate of 10–15% in all stages [5]. Several factors increase the risk of lung cancer. Cigarette smoking is the leading cause of lung cancer [6, 7] and is related to almost 50–90% of cases [2]. Other risk factors are occupational exposure to carcinogens, passive smoking, air pollution, heavy metals, inorganic dusts, chemical compounds [2, 8, 9], airflow abstraction, emphysema [10] and pulmonary fibrosis [11].

The rate of addiction to opium is considerable worldwide. In European countries, the rate of opiate consumption ranges from 2.6 to 21 per 1,000 adult inhabitants [12–15]. In Iran, opium and its derivatives are the most common abusive drugs. In several provinces, the dependency rate reaches an average of 5.3% [16]. In addition, opium is the first illicit substance used by 59% of addicts in Iran [17]. Opium use in Iran consists of teriak (crude opium), shireh (a refined opium extract) [5, 18] and sukhteh (opium dross left in pipes after smoking opium). Teriak and shireh can be smoked or ingested, while sukhteh is usually ingested. Opioid alkaloids increase the susceptibility of humans to different neoplasms such as oral, esophageal and bladder cancers [19]. Although opium has been shown to play an important role in the development of cancers, there is no clear evidence of a link between opium and different types of cancer. This study aimed to investigate the role of opium as a risk factor for developing lung cancer.

Materials and Methods

Between October 2002 and 2005, 242 lung cancer patients with histologically and cytologically confirmed primary lung cancer in five university hospitals in Tehran, Iran, were enrolled in this study as described by Hosseini et al. [8].

For the patients who were referred to our study hospitals, his/her family history of cancer was taken and a physical examination was done by a trained physician. The symptoms of lung cancer, including peripheral lymphadenopathy, abnormal lung sounds and other physical signs, were examined. Primary assessment was performed by taking X-rays and CT scans if clinically necessary. Whenever the CT was abnormal, tissue examination by bronchoscopy or needle biopsy was performed to determine the type of cancer. Bronchoscopy was used when the tumor was located in the large airways and could be reached by the scope. Needle biopsy was performed for tumors which could not be assessed by bronchoscopy.

An expert clinical pathologist reviewed and determined the tumor type according to World Health Organization guidelines [20]. In addition, clinical staging was performed by pulmonologists and radiologists in the National Research Institute of Tuberculosis and Lung Disease (NRITLD) according to the TNM classification [characteristics of primary tumor (T), regional lymph node involvement (N) and metastasis (M)] of the American Joint Committee on Cancer and the Union Internationale Contre Le Cancer [21].

For each case subject, 2 controls matched for age (±3 years), sex and place of residence were selected, one being an in-house patient and the other a healthy visitor. The first control group consisted of patients treated at the hospitals, excluding those with neoplasms and respiratory diseases. The second control group consisted of healthy people visiting other cancer patients. Approximately 91.3 and 91.1%, respectively, of requested cases and controls participated. The Institutional Review Board of the NRITLD approved the present study.

Physicians interviewed all the participants after obtaining informed consent. A detailed structured questionnaire was used to determine basic demographic characteristics, as well as lifelong history of smoking cigarettes, exposure to passive smoking, opium use and alcohol consumption.

Smokers were defined as individuals who had regularly smoked at least one cigarette per day for 6 months. In addition, starting and quitting ages and daily amount with type of cigarette smoked (handmade, domestic or international) were determined.

Opium addiction was defined as consumption of opium at least once a day for a minimum of 6 months. Participants were asked about the route of administration, the age they started and quitted and the frequency of daily use.

In addition, subjects were asked if they had ever regularly consumed alcohol (beer, imported spirits, domestic spirits and others) for 6 months or more.

For cigarettes and opium (smoked and/or ingested), pack years (only for cigarettes), total duration and cumulative use (frequency of daily consumption multiplied by duration of use) were categorized into three groups: no use, low use (≤median use in controls) and high use (>median use in controls). For cigarette smoking status, the median of the study control group was 21 pack years, which seemed a reasonable cutoff for light/heavy smokers based on previous studies [1, 22]. For opium, the median in controls which was used as the cutoff was nearly the same as that used in another study on esophageal cancer in Iran [5]. Age of first use was also categorized into three groups: never used and younger and older than the median starting age in controls. Percentages were tabulated for each of these categories for cases and controls. Then, conditional logistic regression was used to calculate the unadjusted and adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs). In all analyses generally, nonusers were the reference group. P values for trend were obtained from models by assigning the values 0, 1 and 2 to no use, low use and high use, respectively. As education (a rough surrogate marker of socioeconomic status) and ethnicity were found to be potential confounders in preliminary conditional logistic regression, we adjusted for them in bivariate and multivariate analyses. In the case of adjustment for ethnicity, dummy variables were built with Fars as the baseline group. Participants were from eight different ethnic groups, with the majority of the cases and controls being Fars or Azeri. We combined four ethnic groups because of small sample size and categorized ethnicity into five groups. For education, we also categorized participants into five educational levels from illiterate (assigned 1) to more than 12 years of schooling (as-

signed 5). About 52% of cases had studied less than 5 grades. In adjusting for education, it was treated as an ordinal variable in the models. Two-sided p values of <0.05 were considered statistically significant. All statistical analyses were carried out using Stata version 9.0 (StataCorp, College Station, Tex., USA).

Results

A total of 242 cases and their 484 controls matched for age (±3 years), sex and place of residence were recruited into this study over a period of 3 years. Mean ± SD age of cases and controls was 59.9 ± 13.0 and 59.4 ± 12.8 years, respectively (table 1). About 73.6% of the cases and the controls were male. Using conditional logistic regression models, we evaluated potential risk factors for lung cancer in bivariate analyses. Lower education (less than 5 grades) was associated with lung cancer (p value for trend <0.001). Also, lung cancer was more likely in Azeri participants than Fars (OR 1.8, 95% CI 1.2–2.7; p = 0.007). Therefore, we adjusted the following analyses for education and ethnicity.

Smoking cigarettes, as could be predicted, was significantly associated with lung cancer in both men and women (table 2). We also found a positive linear trend across smoking status among men and women with the risk of lung cancer when 0, 1 and 2 were assigned to no use, passive smoker and smoker, respectively, in the analysis ($p < 0.0001$ and $p = 0.04$, respectively). Cumulative lifetime consumption (pack years) and age of starting smoking were significantly associated with lung cancer. Besides, a linear trend was found in the association of lung cancer with pack years of smoking cigarettes in both men and women ($p < 0.0001$ and $p = 0.03$, respectively). These findings were adjusted for education and ethnicity. The unadjusted results are also presented in table 2.

None of the female cases or controls had ever smoked opium. Only 1 female case and 2 controls had ever ingested opium. Therefore, the following findings are reported only in males.

Thirty-three of the male cases (18.5%) and 21 controls (5.9%) had ever smoked opium (table 3). Smoking opium was associated with an increased risk of lung cancer, with an adjusted OR of 7.5 (95% CI 3.4–16.7; table 3). Higher frequency and longer duration of smoking opium and also higher cumulative smoking of opium showed a significantly increased risk of lung cancer. Moreover, we found a significant positive trend in the association of lung cancer with duration of opium smoking ($p < 0.0001$).

In addition, as table 3 shows, 36 male cases (20.2%) and 34 controls (9.6%) had ever ingested opium. In preliminary analysis, ingesting opium significantly increased the risk of lung cancer, with an adjusted OR of 2.2 (95% CI 1.3–3.8). Also, higher frequency of use, duration of use, higher cumulative ingestion of opium and younger age of first use all showed a significant association with an increased risk of lung cancer (unadjusted and adjusted ORs and corresponding 95% CIs are shown in table 3). A positive trend was observed among individuals who ingested opium more frequently with lung cancer ($p < 0.0001$). We also found a significant risk of lung cancer in individuals who both smoked and ingested opium; the adjusted ORs (95% CI) for smoking opium only and ingesting opium only and both were 5.4 (2.1–14.0), 1.4 (0.7–2.7) and 13.7 (4.2–44.0), respectively.

Alcohol consumption is not common in Iran, since by law it is prohibited [23]. Forty-four of the male cases (24.7%) and 72 of the controls (20.2%) had ever used alcohol for 6 months or more, and the adjusted and unadjusted ORs were 1.7 (95% CI 1.05–2.81; p = 0.03) and 1.3 (95% CI 0.8–2.0; p = 0.23), respectively. Only 1 female case and 3 controls were alcohol consumers.

Table 1. Demographic characteristics of cases and matched controls

Characteristic	Cases	Controls
Number	242	484
Age, years[1]		
Male	61.3 ± 12.3	60.8 ± 12.1
Female	55.9 ± 14.2	55.4 ± 14.0
Total	59.9 ± 13.0	59.4 ± 12.8
Sex		
Male	178 (73.6%)	356 (73.6%)
Female	64 (26.4%)	128 (26.4%)
Marital status		
Married	218 (90.1%)	456 (94.2%)
Unmarried	24 (9.9%)	28 (5.8%)
Ethnicity		
Fars	109 (45.0%)	256 (52.9%)
Azeri	83 (34.3%)	129 (26.7%)
Kurd	10 (4.1%)	21 (4.3%)
Lur	8 (3.3%)	24 (5.0%)
Other	32 (13.3%)	54 (11.1%)
Education		
Nil	99 (40.9%)	118 (24.4%)
<5 years	27 (11.2%)	52 (10.8%)
5–8 years	63 (26.0%)	122 (25.2%)
8–12 years	46 (19.0%)	125 (25.8%)
>12 years	7 (2.9%)	67 (13.8%)

Values represent numbers of patients (percentage), except where indicated otherwise.

[1] Mean ± SD.

Table 2. Smoking status, cumulative lifetime consumption of cigarettes (pack years) and age of first use in cases and controls

Characteristic	Cases	Controls	Unadjusted OR	Adjusted OR[1]
Males				
Smoking category				
Nonsmoker	17 (9.5%)	127 (35.7%)	reference	reference
Passive smoker	9 (5.1%)	43 (12.1%)	1.5 (0.6–3.6)[3]	1.7 (0.7–4.3)
Smoker	152 (85.4%)	186 (52.2%)	6.0 (3.4–10.6)	6.2 (3.3–11.6)
				p for linear trend < 0.0001
Pack years				
Never smoked	26 (16.1%)	170 (55.1%)	reference	reference
≤Median[2]	19 (11.7%)	81 (24.6%)	1.1 (0.6–2.0)	1.8 (0.8–3.9)
>Median	117 (72.2%)	79 (23.9%)	10.0 (5.6–17.9)	13.6 (6.5–28.5)
				p for linear trend < 0.0001
Age started				
Never smoked	26 (15.0%)	170 (51.5%)	reference	reference
>Median[2]	70 (40.5%)	71 (21.5%)	6.7 (3.8–11.7)	7.3 (3.8–13.9)
≤Median	77 (44.5%)	89 (27.0%)	5.7 (3.3–9.7)	5.2 (2.9–10.0)
Females				
Smoking category				
Nonsmoker	26 (40.6%)	68 (53.1%)	reference	reference
Passive smoker	29 (45.3%)	51 (39.8%)	1.5 (0.8–3.0)	1.4 (0.7–2.9)
Smoker	9 (14.1%)	9 (7.1%)	3.1 (1.0–9.6)	3.1 (1.0–10.9)
				p for linear trend = 0.04
Pack years				
Never smoked	55 (85.9%)	120 (93.8%)	reference	reference
≤Median[2]	1 (1.6%)	4 (3.1%)	0.4 (0.04–4.6)	0.7 (0.05–9.3)
>Median	8 (12.5%)	4 (3.1%)	6.6 (1.4–31.8)	6.1 (1.2–30.0)
				p for linear trend = 0.03
Age started				
Never smoked	55 (85.9%)	119 (93.0%)	reference	reference
>Median[2]	4 (6.3%)	4 (3.1%)	2.3 (0.6–9.4)	2.5 (0.6–10.7)
≤Median	5 (7.8%)	5 (3.9%)	2.5 (0.6–9.7)	2.9 (0.7–12.8)

[1] Adjusted for education and ethnicity. [2] We used the median in the control group as the dividing point. [3] 95% CIs.

We tested important interactions, such as smoking cigarettes with ingesting opium and smoking opium with ingesting opium, which were found to be not significant ($p = 0.26$ and $p = 0.42$, respectively). Due to zero cells, evaluating the interaction of smoking cigarettes and smoking opium was not possible.

In a multivariate conditional logistic regression analysis, we simultaneously entered cumulative lifetime consumption of cigarettes (pack years), smoking and also ingestion of opium and consumption of alcoholic beverages as predictors while adjusting for education and ethnicity. Then, we used backward stepwise elimination. In the results, only pack years of smoking cigarettes and smoking opium remained significant independent risk factors of lung cancer development (table 4). Since the trend for pack years of smoking cigarettes was significant, it was treated as an ordinal variable in the model, with values of 0, 1 and 2 for no use, low use and high use, respectively. According to this model, the risk of lung cancer in heavy cigarette smokers and concomitant opium use and heavy cigarette smoking was computed as 11.3 (95% CI 5.4–23.8) and 35.0 (95% CI 11.4–107.9), respectively.

Discussion

Our study showed that smoking opium is associated with a risk of lung cancer when adjusted for education, ethnicity and smoking cigarettes. With concomitant smoking of cigarettes and opium, the risk of lung cancer development increases dramatically.

Table 3. Opium use (smoked or ingested), age of starting and route of administration in male cases and controls

Opium consumption	Cases, n	Controls, n	Unadjusted OR	Adjusted OR
Smoking opium				
Never	145 (81.5%)	335 (94.1%)	reference	reference
Ever	33 (18.5%)	21 (5.9%)	4.8 (2.4–9.6)[7]	7.5 (3.4–16.7)
Frequency of use				
Never used	145 (81.5%)	335 (94.1%)	reference	reference
≤Median (twice a day)[1]	30 (16.8%)	17 (4.8%)	4.9 (2.4–10.0)	7.7 (3.4–17.4)
>Median	3 (1.7%)	4 (1.1%)	3.2 (0.6–16.0)	5.3 (0.8–36.8)
				p for linear trend < 0.0001
Duration				
Never used	145 (81.5%)	335 (94.4%)	reference	reference
≤Median (20.5 years)[2]	11 (6.2%)	10 (2.8%)	3.9 (1.4–11.0)	6.6 (2.1–21.0)
>Median	22 (12.3%)	10 (2.8%)	6.2 (2.6–14.3)	9.6 (3.6–25.6)
				p for linear trend < 0.0001
Cumulative use				
Never used	145 (81.5%)	335 (94.4%)	reference	reference
≤Median (36.5 n/day-years)[3]	18 (10.1%)	10 (2.8%)	5.4 (2.2–13.0)	9.6 (3.5–26.8)
>Median	15 (8.4%)	10 (2.8%)	5.1 (1.9–13.4)	6.9 (2.3–20.4)
				p for linear trend < 0.0001
Oral opium intake				
Never	142 (79.8%)	322 (90.5%)	reference	reference
Ever	36 (20.2%)	34 (9.6%)	2.3 (1.4–3.7)	2.2 (1.3–3.8)
Frequency of use				
Never used	142 (84.0%)	322 (94.7%)	reference	reference
≤Median (once a day)	13 (7.7%)	16 (4.7%)	1.6 (0.8–3.3)	1.5 (0.7–3.4)
>Median	14 (8.3%)	2 (0.6%)	13.1 (3.0–57.7)	17.5 (3.4–89.8)
				p for linear trend < 0.0001
Duration				
Never used	142 (79.8%)	322 (91.4%)	reference	reference
≤Median (23 years)[4]	24 (13.5%)	15 (4.3%)	3.3 (1.7–6.3)	3.8 (1.8–7.8)
>Median	12 (6.7%)	15 (4.3%)	1.8 (0.8–4.0)	1.6 (0.7–3.8)
				p for linear trend = 0.008
Cumulative use				
Never used	142 (84.2%)	322 (94.5%)	reference	reference
≤Median (23 n/day-years)[5]	13 (10.7%)	13 (3.7%)	2.8 (1.2–6.6)	3.8 (1.5–9.9)
>Median	14 (9.1%)	9 (4.8%)	2.9 (1.3–6.8)	2.5 (1.01–3.2)
				p for linear trend = 0.003
Age at start of opium use				
Never used	142 (80.2%)	322 (91.5%)	reference	reference
>Median (35 years)[6]	19 (10.7%)	13 (3.7%)	3.3 (1.5–7.0)	2.9 (1.3–6.5)
≤Median	16 (9.1%)	17 (4.8%)	2.0 (1.0–4.1)	2.4 (1.1–5.1)
				p for linear trend = 0.003
Route of administration				
Never used	127 (71.4%)	307 (86.2%)	reference	reference
Ingested opiate only	18 (10.1%)	28 (7.9%)	1.5 (0.8–2.8)	1.4 (0.7–2.7)
Smoked opiate only	15 (8.4%)	15 (4.2%)	3.2 (1.4–7.5)	5.4 (2.1–14.0)
Both	18 (10.1%)	6 (1.7%)	9.0 (3.2–25.2)	13.7 (4.2–44.0)
				p for linear trend < 0.0001

[1–6] We used the median in the control group as the dividing point. [7] 95% CIs.
[3,5] n/day-years = number of daily consumption multiplied by duration (years).

Table 4. The association between smoking cigarettes and/or opium and lung cancer (adjusted for education and ethnicity)

Risk factor	Unadjusted β	Adjusted β[1]	OR[1]	p value[1]
Pack years of smoking cigarettes	1.27 (0.18)	1.21 (0.19)	3.4 (2.3–4.9)	<0.0001
Smoking opium	0.58 (0.43)	1.12 (0.49)	3.1 (1.2–8.1)	0.02

Figures in parentheses are standard errors or 95% CIs, as appropriate.
[1] Adjusted for education and ethnicity.

To the best of our knowledge, this is the first study worldwide that has investigated the effect of smoked opium in relation to lung cancer. One study only looked at the effect of ingested opium on lung cancer but did not consider smoked opium at the same time [24]. We considered some possible confounders in the design of our study by matching cases and controls and adjusting for some other confounders elicited from our data. In our study, we chose our controls in such a way that we thought if they had lung cancer they would have been referred to the hospitals from which we recruited our cases. However, it is still possible that the control group may be biased, as any hospital-based retrospective case-control study is subject to a number of confounders, such as selection bias, reporting bias and interviewer bias. Given that lung cancer patients may respond more truthfully to questions about opium use than controls chosen from visitors, reporting bias might be possible. Also, as the interviewers were physicians and they were most likely aware of the diagnosis of the patients, interviewer bias cannot be totally ruled out. The method of exposure assessment for illegal products, i.e. opium and alcohol consumption, and the presence of misclassification bias due to a difference between cases and controls in reliably and truly self-reporting any history of their consumption could be another possible source of bias.

Moreover, in this case-control study we only evaluated opium smoking addiction in men since no women were opium smokers. Therefore, the results of this study possibly can be generalized only to men. Since there is a general belief that women in Iran are reluctant to declare their recreational drug usage, the prevalence of addicted women may be underestimated in all studies [25, 26]. This may be why we did not find any women addicted to smoking opium in our study. Indeed, we think there may have been some women in this category but they denied their abuse of opium.

Our data showed no relation between alcohol consumption and lung cancer in multivariate analysis, although it was significant in models which did not consider cigarettes and opium smoking. According to previous studies, the relation between alcohol intake and lung cancer is controversial [27].

Our findings showed that smoking of opium is associated with an increased risk of lung cancer. A significant association between opium consumption and several types of organ cancers (oral, esophageal and bladder) has been revealed recently [19, 28, 29], but there is a paucity of studies investigating the relation between opium use and lung cancer. This finding is very important because opium addiction is highly prevalent among cigarette smokers [30, 31]. Nasrollahzadeh et al. [5] conducted a similar study into the relation between cigarette smoking and opium use and esophageal squamous cell carcinoma and found concomitant use to be a risk factor for esophageal cancer (OR 2.35, 95% CI 1.50–3.67). However, our study shows that concomitant smoking of cigarettes and opium use could be a more severe risk factor for development of lung cancer than esophageal squamous cell carcinoma. Several mechanisms have been proposed for the involvement of opium in the development of different cancers. It has been shown that pyrolysate (a substituted hydroxyphenanthrene in opium particularly of morphine) is highly mutagenic since it can induce sister chromatid exchanges in mammalian cells after metabolic activation [19]. Morphine has also been linked to carcinogenesis by increasing the ethylation of DNA through reduction of N-nitrosamines and N-nitrosodimethylamine first pass clearance by the liver [19, 32]. Although cigarette smoking has been definitely linked to lung cancer, there is much to be discovered about the etiology [33]. We showed that opium smoking may have a role in the development of lung cancer. Other studies should investigate its role to further confirm this.

In conclusion, this study showed that smoking opium is associated with a high risk of lung cancer as an independent factor. In addition, its additive effect with cigarette smoking dramatically increases the risk of lung cancer.

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Financial Disclosure and Conflicts of Interest

The authors declare that they have no competing interests.

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