Opium as a Risk Factor for Bladder Cancer: A Population-based Case-control Study in Iran

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Abstract

Background: Bladder cancer (BC) is the most common genitourinary system malignancy in humans. Consumption of opium and its derivatives, maybe a risk factor possibly in Iran. The aim of this study was to investigate the relationship between consumption of opium and its derivatives and the incidence of BC.

Methods: In an individually matched case-control study in Shiraz (located in the south of Iran), 198 patients with BC and 396 healthy individuals (matched in age, sex and residence (urban/rural)) were investigated. Data about consumption of opium and its derivatives, tobacco, alcohol and diet were collected using a structured valid and reliable questionnaire. Crude and adjusted odds ratios (ORs) were computed using conditional logistic regression models.

Results: Opium consumption was associated with an increased risk of BC with an adjusted OR = 3.9 (95% CI: 1.2 – 12.0). Moreover, a considerable dose-response relationship was observed between the opium consumption and its derivatives and the incidence of BC; comparing to no users, the odds ratios of low and high consumptions were 3.3 (95% CI: 0.5 – 23.1) and 4.9 (95% CI: 1.1 – 21.9) respectively.

Conclusion: Opium consumption can be a potential strong risk factor for BC in Iran.

Keywords: Bladder neoplasms, case-control, Iran, opium, risk factor

Introduction

Bladder cancer (BC) is the most common genitourinary system malignancy, the third most common cancer in Iranian men,[1] and the ninth most common in Iranian women.[2] According to the global report of cancer in 2008, after lung cancer, BC is the most common cancer among men.[3] This was confirmed by the report by the Center of Disease Control and Prevention in 2005, which states that BC constitutes 7.04% of all cases of cancer in Iran.[4]

According to information from the Cancer Registry of Shiraz University of Medical Sciences, BC was the fifth most common cancer among men in Fars province between 1989 and 1991, and currently it has become the second one in the list in this province.[5] The age standardized annual incidence of BC in Fars province between 2003 and 2008 was reported 6.9, 6.5, 11.2, 10.0, 12.6 and 10.3 cases per one hundred thousand respectively, which shows an increasing trend.[6]

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There are several known risk factors for this cancer. Similar to many other malignancies, environmental and behavioral factors are very important risk factors in the occurrence of BC. Among these behavioral risk factors, opium consumption might potentially increase the risk of BC. Regular use of opium has been recognized as a risk factor for many diseases, including some types of cancers.[7] Previous studies have found some evidences about the association between opium use and the risk of many cancers such as larynx,[8] lung,[9] gastric,[10,11] esophagus,[7,12] and bladder.[13,14]

The prevalence of opioid consumption varies between 0.1% to 2% in the world.[15] Iran has several hundred years history of opium use, a high prevalence of opioids use, which is the most common form of drug abuse in Iran.[16] It was reported that in 2003, about 1.2 million addicts lived in Iran, and this number might increase by 8% each year.[17] This increase is more concentrated in the north and south of the country.[18,19] A study conducted on the general population of Fars Province in 2003 revealed that 8.8% of the population was opium users[20] and along with this high frequency of consumption, an increase in the occurrence of BC was also observed.[5]

Various studies have revealed that opium and its derivatives are among the most important risk factors for BC.[13,14] A study in Kerman, Iran, demonstrated that opium abuse increased the risk of BC, 7.9 times.[21] In another study, the prevalence of opium consumption in BC patients was reported 33.5 percent, while it was 3.9 percent in the controls (adjusted OR = 4.6).[13]

Based on the above explanation, the frequency of opium consumption in the south of Iran, such as Fars Province is high. Therefore, deeper exploration might be needed to quantify the association of opium use and BC. Based on this justification, we designed a case-control study to assess the possible connotation between opium use and the incidence of BC.

Materials and Methods

Selection of cases and controls

This study was carried out in a big city in the south of Iran, Shiraz, the capital of Fars province, with a population of 1,460,665 in year 2011, and the dominancy of Persian ethnicity.

This project was a population based individually matched case-control study. Newly diagnosed cases were tracked based on the records of the cancer registry in 2012 and 2013, mainly based on the results of the pathology, sometimes followed by their hospital records. For every case, two age and gender matched neighborhood controls were recruited concurrently.

To calculate the sample size for a matched case control study, a minimum sample size of 196 was calculated.

Cases and/or their families were approached through phone calls to schedule an interview in their home. Those who did not respond to frequent calls were approached in their homes to minimize the number of non-responses.

Matched controls (based on gender and age (± 5 years) were recruited from the neighbors of cases systematically; from the residents of the nearest neighbors on the right side of each case, the eligible controls were approached. Having explained the main objectives of the study to cases and controls, their consents were taken before the formal interview in their living places.

Data collection

The data collection tool was a structured questionnaire consisting of three parts including: 1) demographic information, including gender, age, the education level and marital status, 2) information about their possible confounders such as their diet, and 3) information about the dose and method of opium, opioid, alcohol, and tobacco consumption. The validity and reliability of the questionnaire was evaluated in previous studies.[22,23]

To minimize the bias resulting from inter-observer variation, almost all interviews were carried out by the main researcher. In order to quantify the level of opium and its derivatives use, as well as tobacco use, the details of the current and past history consumptions of subjects were questioned. The cumulative lifetime use was computed based on the amount and the duration of consumptions in different ages to take into consideration of any fluctuation in their status over time. Daily consumption doses were based on the local unit "Nokhod," which contains 0.2 grams. Opioids were also categorized into four groups; teryak (raw opium), shireh (opium sap), sukhteh (burned opium) and heroin.

To minimize the level of under-reporting of opium use, particularly in controls, the questions about opium use were asked at the end of the interview; and the interviewer learned how to communicate with different personalities in advance to create a calm and friendly environment during the conversation.

Since cases of heroin and burnt opium abuse were very few, the two kinds of opioids, raw opium and opium sap were combined and merged in data analysis. Since malignant cells require a long period of induction to be formed, the questions regarding the diet were designed for a time span starting 10 to 20 years prior to the time of interview. The diet section of the questionnaire contained questions about common Iranian diets and especially that of local people of that area. The present study was approved by the Ethical Committee of Kerman University of Medical Sciences. Also the interviews were conducted after obtaining verbal informed consent from subjects or their relatives.

Statistical analysis

The cumulative consumption of tobacco and opium were computed based on the amount of daily use and the duration of consumption over their life. Then subjects were categorized as no use, low use and high use. The median of use of controls was set to discriminate low from high use subjects. In addition, current user was defined if subjects have a history of substance abuse in the recent year. Due to the low prevalence of alcohol consumption, the variable was converted to two-state consumers and non-consumers in the final analysis. However, to minimize the impact of reverse causality in cases; the history of usage was taken before the diagnosis of their malignancies. Conditional logistic regression was used to compute the crude and adjusted ORs between the risk of BC and consumption of opium, alcohol and tobacco. Only those variables with P-value less than 0.1 in the simple model were added in the final multivariate model. All statistical analysis was carried out using stata11 (Stata Corp, College Station, TX, USA).

Results

At the end, 21subjects (cases and controls) refused to participate in this study (non-responserate10.6%). In cases, 75.3% were men, 54.6% were aged between 51 and 70 years, and more than 50% had 0 to 5 years of education (Table 1).

The mode of age for the first experience of tobacco and opium use was less than 20 and 20 – 30 years respectively. Among opium users, in average subjects had consumed 21.8 years (SD = 12.3), and smoking was the most common method of use among cases (87.7 %) and controls (75.6%), ($P < 0.001$)

Overall, 21.7 % of cases and 4.6% of controls had a history of opium consumption, ($P < 0.001$).

Table 2 shows the results of opium, tobacco and alcohol consumptions. The adjusted odds ratio of opium use was 3.9 (95% CI: 1.3 – 12.0); 51.5% of the cases group were tobacco user, while this was 20.7% (82 people) in the controls. The findings revealed that after adjusting for potential confounding variables such as diet, tobacco use and alcohol consumption, the adjusted odds ratio for daily opium consumption was 2.4 (0.6 – 9.4). Also, this study revealed that the duration of opium more than median has the OR of 6.0 (95% CI: 1.1 – 34.7). Also, cumulative consumption of opium with an adjusted odds ratio of OR = 4.9 (95% CI: 1.1 – 21.9) had a considerable relation with developing BC, which shows the presence of a dose-response relationship between opium use and BC.

Tobacco use, both in simple logistic regression (OR = 4.0 (95% CI: 2.7 – 5.9) and multi-variable analysis (OR = 2.5 (95% CI: 1.3 – 4.8), showed to have a relation with BC. Furthermore, daily tobacco use had a significant relation with developing BC, OR = 5.3 (95% CI: 2.3 – 12.0). The duration of tobacco use more than median has the OR of 3.5 (95% CI: 1.6 – 7.4), and cumulative tobacco use also had a significant relation with it OR = 4.9 (95% CI: 2.2 – 11.1). Due to the possibility of a co-linearity between the cumulative use of tobacco and opium, we checked the variance inflation factor (VIF). It was 0.29 and 0.27 in two models without and with the variety of tobacco use that shows there is not co-linearity effect between these two independent variables.

Among our subjects, 12.1% of cases and 4.0% of controls reported a history of alcohol consumption. The difference between the cases and controls in alcohol consumption was statistically

Table 1. Demographic information of cases and controls

Variables	Matched controls, N (%)	Bladder cancer, N (%)	*P- value
N	396	198	
Gender			
Male	298 (75.3)	149 (75.3)	0.99
Female	98 (24.7)	49 (24.7)	
Marital status			
Married	394 (99.5)	197 (99.5)	0.85
Single	2 (0.5)	1 (0.5)	
Age			
Mean (SD)	65.9 (11.5)	66.2 (11.9)	
< 50	37 (9.3)	18 (9.0)	0.12
51–70	228 (57.7)	108 (54.6)	
> 70	13 (33.0)	72 (36.4)	
Education(year)			
0–5 year	247 (62.8)	110 (55.5)	< 0.001
6–11 year	132 (33.3)	66 (33.4)	
≥ 12 year	17 (3.9)	22 (11.1)	
*Significant at the 0.05 level			

Table 2. The ORs between bladder cancer and using opioid derivatives, cigarette and alcohol

Variable	Cases- N (%)	Controls- N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*
Opium				
Opium use				
Never	155 (78.3)	378 (95.4)	Referent	Referent
Ever	43 (21.7)	18 (4.6)	5.8 (3.2–10.5)	3.9 (1.3–12.0)
Amount of daily use				
Never used	155 (78.3)	378 (95.4)	Referent	Referent
≤ Median**	17 (8.7)	10 (2.6)	3.8 (1.7–8.8)	4.4 (0.5–33.5)
>Median	26 (13.0)	8 (2.0)	8.5 (3.5–20.7)	2.4 (0.6–9.4)
Duration				
Never used	155 (78.3)	378 (95.4)	Referent	Referent
≤ Median	17 (8.6)	10 (2.5)	4.2 (1.8–9.6)	2.5 (0.5–11.3)
>Median	26 (13.1)	8 (2.1)	7.4 (3.3–16.7)	6.0 (1.1–34.7)
Cumulative use of Opium***				
Never used	155 (78.3)	378 (95.4)	Referent	Referent
≤ Median	12 (6.0)	9 (2.3)	3.3 (1.3–8.3)	3.3 (0.5–23.1)
>Median	31 (15.7)	9 (2.3)	7.9 (3.6–17.3)	4.9 (1.1–21.9)
Tobacco use				
Cigarette smoking				
Never	96 (48.5)	314 (79.3)	Referent	Referent
Ever	102 (51.5)	82 (20.7)	4.0 (2.7–5.9)	2.5 (1.3–4.8)
Amount of daily use				
Never used	96 (48.5)	314 (79.3)	Referent	Referent
≤ Median	25 (12.6)	54 (13.6)	1.6 (0.9–2.8)	1.1 (0.4–2.6)
> Median	77 (38.9)	28 (7.1)	8.2 (4.9–13.9)	5.3 (2.3–12.0)
Duration				
Never used	96 (48.5)	314 (79.3)	Referent	Referent
≤ Median	22 (11.1)	43 (10.8)	1.6 (0.9–3.0)	1.4 (0.5–3.6)
> Median	80 (40.4)	39 (9.9)	6.5 (4.0–10.6)	3.5 (1.6–7.4)
Cumulative use of smoking				
Never used	96 (48.4)	314 (79.3)	Referent	Referent
≤ Median	17 (8.6)	43 (10.8)	1.4 (0.7–2.6)	1.0 (0.4–2.8)
> Median	85 (43.0)	39 (9.9)	6.6 (4.1–10.6)	4.9 (2.2–11.1)
Alcohol				
Alcohol use				
Never	174 (87.9)	380 (95.9)	Referent	Referent
Ever	24 (12.1)	16 (4.1)	3.5 (1.7–7.1)	2.9 (1.2–7.1)

*Nutritional factors, such as red meat, poultry, fish, hydrogenated oil, olive oil, butter intake, fat intake, fruits, nuts consumption, moldy food, alcohol and tobacco use variables were controlled; **Median use in the controls was taken as the cutoff point; ***Cumulative use was calculated by multiplying the average use (per day) by consumption period (in years).

significant, in both simple logistic regression (OR = 3.5 (95% CI: 1.7 – 7.1) and multi-variable analysis OR = 2.9 (95% CI: 1.2 – 7.1), (Table 2).

Discussion

In this study, the relation between opium use and BC was investigated. According to our findings, the opium consumption increases the risk of BC. Carcinogenicity of opium is affected by different factors, including daily dosage, duration of consumption, age, and the method of consumption.[21]A strong dose-response relationship was observed between opium consumption and BC and this finding is compatible with the findings of other similar studies.[13,21]

In the present study, the BC odds ratio was 3.3 in the group with low opium consumption, and 4.9 in the high opium-consuming group. Findings of various studies conducted in Iran were more or less similar. For instance, a study in Kerman province between 1999 and 2003, demonstrated that the incidence of BC in opium users was 7.9 times more than the controls.[21] In another study by Hosseini, et al. in 2008, it was observed that opium use increased the adjusted odds ratio of BC five times.[13] The same association was also observed with other type of cancers such as upper gastro-intestinal, OR = 4,[24] and larynx cancers, OR = 11.[8]

Nevertheless, many mechanisms for the carcinogenicity of opium are not well known yet. Many research groups have investigated the mechanisms of opium carcinogenicity and several mechanisms have been suggested including alkaloids present in opium such as morphine, which could have mutagenic properties. Six carcinogens were also extracted from opiates by thermal decomposition, of which the most important are nitrosamine and diethylnitrosamin.[25,26] It is important to mention that to increase their profit, dealers and distributors are usually add extra material to increase the weight of drugs. Some of these added materials contain toxic substances such as lead compounds which might have carcinogenic effect as well.[27–29]

Among an estimated 16.5 million people who have been reported to use illegal drugs worldwide, 4 million take opium.[30]As mentioned before, there are more than one million opium abusers in Iran. In addition, it seems that the opium consumption is relatively more common in the eastern provinces of Iran than other ones. Drug abuse in Fars province, has also an alarming rate. According to a study in 2007 in Fars province, 17.9 percent of the participants had a history of opium abuse, and 8.8 percent were current abusers.[20]

Tobacco use is one of the most important risk factors in BC.[31,32] In this study, a significant association was observed between the cases and controls regarding tobacco use, which confirms the findings of previous studies.[13,14,32] In a study by Asgari, the risk of BC was observed to be 3.8 times more in smokers.[33] In other studies, the population attributable risk for tobacco use, as the most well known risk factor, was reported to be 50 to 70 percent for men and 20 to 30 percent for women.[34,35]

Another potential BC risk factor is alcohol consumption. In this study, we observed a direct relationship between alcohol consumption and the risk of BC, which are compatible with the findings of a study in Netherland on the same subject. However, in another study it was shown in the United States, people who consume alcohol at least four times a day had 32 percent lower risk of BC.[36,37] Due to these discrepancies, more research might be needed to explore the impact of alcohol consumption and the risk of BC.

It seems that the present study is the first population-based study in Iran, which was carried out in an individually matched manner. By now, most of the studies conducted on this subjects were selected their cases and controls in hospitals and without matching individually.[13,21]

However, this study had some limitations, like any other case control study; it could be prone to different biases such as interviewer and recall bias. Under-reporting of opium use, especially in the controls could potentially cause bias in the results. However, by standardizing the interview procedure and training of interviewers, we tried to minimize these biases.

This article has a lot of strengths, including the selection of patients based on histopathology, also in this study; we only used the data of incidence cases. In addition, individual matching minimized the impact of residual confounders. Although the selection of controls from the neighbors of cases was very difficult, we expect the impact of environmental risk factors and socioeconomic status of subjects do not change the reported associations significantly.

In conclusion, a strong relation was observed between the use of opium and BC, which makes opium a major potential risk factor for BC in Iran. Considering the high consumption of opium in Iran and the increase in the occurrence of different types of cancers, such as BC, especially in men; implementing prevention programs and policies may promote the awareness of the community.

Acknowledgments

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