

Original Article

Opium as a Risk Factor for Upper Gastrointestinal Cancers: A Population-based Case-Control Study in Iran

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Abstract

Background: Gastrointestinal cancers, including esophageal, gastric, liver and pancreatic are relatively common in Iran. Furthermore, consumption of opium and its derivatives (O&D) are considerable. This study, aimed to examine the association between consumption of O&D and the incidence of upper gastrointestinal (UGI) cancers.

Methods: In a matched case-control study in Kerman (located in southeast of Iran), 142 patients with UGI cancers and 284 healthy people (matched in terms of age, sex and residence (urban/rural)) were recruited. Variables (using O&D, smoking, alcohol use and diet) were collected using a structured questionnaire. Conditional logistic regression models were used to assess the above mentioned association.

Results: Opium use was associated with an increased risk of UGI cancers with an adjusted OR 4.0 (95 % CI: 2.2 – 7.0). A very strong dose-response relation was observed between consumption of O&D and the incidence of UGI cancers. (Three consumption levels-none, low and high; OR = 18.7; 95 % CI: 5.5 – 63.3). This dose-response relationship was also strong even in patients with gastric cancers (OR: 9.2; 95 % CI: 2.5 – 33.7).

Conclusion: The results of this study showed that opium consumption can be a strong risk factor for UGI cancers in Iran.

Keywords: Case-control, Iran, opium, risk factors, UGI neoplasms

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Introduction

UGI cancers are among the most common cause of deaths in the world. Following lung cancer, gastric cancer has the second rank in the world in terms of mortality.¹ The UGI tract includes the oral cavity, esophagus, stomach, liver, and pancreas.² In Iran, these cancers are still considered as one of the most important cancers and cause of death. In recent years, cancer registry findings in Iran have shown that more than 60 percent of deaths from cancer are attributable to UGI,³ with gastric cancer, hepatic and bile duct cancers, and esophageal cancer having the highest mortality rates among all other cancers.⁴

Moreover, there is obvious geographic diversity in the incidence of UGI cancers in Iran. This shows that the risk factors for these cancers are different in various parts of Iran. Iran is one of the countries where UGI cancers is higher than the other parts of the

world, with its northern parts especially Golestan province being one of the high-risk regions in the world.⁵⁻⁷ In Kerman province, the largest province of Iran, located in the southeast of the country, GI cancers is also the most common cancers in recent years with an increasing trend; that is, among them, gastric cancer was the most common form among men and the second most common form among women.⁸ In addition, in recent years, the incidence of liver cancer has increased in Iran. It should be also noted that the incidence of this cancer in Kerman is around three times higher than the national average.⁹

Regular uses of opium have been recognized as a risk factor for many diseases including some cancers. Previous studies have found some evidence about the association between opium use and the risk of many cancers such as larynx, lung and bladder.¹⁰⁻¹³ Recently, a few studies have pointed to the association between opium use, and esophageal and gastric cancer, but generally there is little epidemiological findings about the association between opium use and UGI cancers.¹⁴⁻¹⁷ Nowadays, around 15 million people worldwide take opioids. Opium is traditionally used in many south-central Asian countries, especially Iran, Pakistan, Afghanistan and India, as well as in some areas of South-East Asia.¹⁶ In Iran opioid use is more prevalent in the northern and southern parts.^{18,19} In a study carried out in Golestan province (north of Iran where the incidence of esophageal cancer is high) showed that 17 % of people aged more than 40 used opioids,¹⁶ and this might contribute to the high rates of esophageal cancer in this area.¹⁴ In the north of Kerman the incidence of UGI cancers was relatively high,⁸ and opium consumption is the most common form of drug abuse.¹⁸ It was found in a study in Kerman that the urine test of 15 % of the subjects who were referred to one of the major

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medical diagnostic laboratories was positive.¹⁹

A cross-sectional study conducted in Golestan Province on the effect of opium use as a risk factor of esophageal cancer, found that men used opium more than women, and villagers more than city dwellers; this may be related to the increased rate of esophageal cancer in men and villagers of this region.⁷

The high consumption of opium in Iran especially in Kerman, is probably due to its adjacency to Afghanistan, the most important opium producer in the world which facilitates the availability of opium. This fact in addition to the high incidence of UGI cancers, particularly in the northern parts of Kerman Province led us to design a case-control study to explore the possible association between opium use and the incidence of UGI cancers.

Materials and Methods

Selection of subjects and controls

In this matched case-control study, 142 patients with UGI cancers (oral cavity, liver, esophagus, stomach, or pancreas) were selected from the northern part of Kerman based on the pathological data records at the cancer registry of Kerman province from August 2010 to November 2012. Hospital-based information was also re-checked to ensure that all eligible patients were detected. In order to calculate the sample size, the following assumptions were set: the minimum desired odds ratio of 2, the frequency of opium use in the general population 0.2, the ratio of numbers of control per case 2 : 1, the statistical power and the alpha error 0.8 and 0.05 respectively. Using these assumptions, a minimum sample size of 150 was calculated.

The patients' information including the home address, the phone number and type of cancer were extracted from their medical records.

A date was set with cases or their close relatives in advance via their phone numbers. For every subject, two neighborhood controls were selected, matched in terms of gender and age. In a systematic way, for each case, we approached the nearest two right-side neighbors and checked for any eligible matched controls; with the same method we approached more neighbors if we did not find matched controls in the first two houses.

Data collection

The data collection tool was a questionnaire which consisted of two parts. The first part asked the demographic information including gender, age and education; the second part focused on the history of opium, alcohol, smoking and diet. The validity and reliability of the questionnaires were checked in previous studies.^{20,21} To minimize the bias resulting from inter-observer variation, almost all of interviews were conducted by the main researcher. Also in order to minimize the level of under-reporting of opium use in the control group, a trained interviewer explained the objectives of the study to all interviewees clearly and convinced them that their responses would be used only in this project. Interviews were carried out in a calm and friendly environment to maximize the contribution of interviewees. The questionnaire covered life-long history of tobacco use, including smoking cigarettes, using opium, and in each daily amount used.

We divided the lifetime into different age-bands and from each one the type and the amount of opium consumptions were asked. Daily consumption of opium was based on a local measurement unit, "Nokhod"; every Nokhod contains 0.2 grams. We categorized opium type in four main groups:

1) teriak (raw opium), 2) shireh (opium sap), 3) sukhte (burned opium), 4) heroin. No subject was a sukhteh or heroin user. Therefore, for analysis we pooled two types of opium use (raw opium and opium sap). Therefore, for analysis, we merged the use of all types of opium together.

Dietary questionnaire included foodstuff used typically in the Iranians diets especially in this region. All interviews were conducted at the interviewees' houses and in a relaxing environment. If the subject was alive, interviews were mostly conducted face to face; otherwise, the closest family member was interviewed.

This study was approved by the Ethical Committee of Kerman University of Medical Sciences. Interviews were conducted after taking a verbal informed consent from subjects or their relatives.

Statistical analysis

For each exposure (tobacco and opium), the cumulative consumption (average daily use multiplied by the duration of use) was calculated, and divided into three subgroups of non-use, low use (\leq median use in the controls) and high use ($>$ median use in the controls). Since median use in controls probably represented the consumption in the entire population, it was considered as the cut off point for classification of the amount of consumption. In all analyses, the non-use group was set as the reference group.

In this study, some subjects started using opioids after the diagnosis of cancer. Thus, to minimize the effect of reverse causality, only records of opioid use prior to the disease diagnosis were recorded. Because of the low incidence of alcohol use, it was classified into two groups: with and without the history of consumption. However, since almost all of subjects were Muslim, the alcohol use was very low.

In this analysis, three outcomes were modeled 1- all cancers, 2- gastric cancer, and 3- The other cancers (oral cavity, liver, pancreas and esophagus). As compared with the other high enough UGI cancers, the numbers of gastric cancers were relatively high enough to be able to analysis its data separately. In order to calculate odds ratio (OR) in the univariate and multivariate analyses, conditional logistic regression was used to matched cases with their controls. In all multivariate models, only the confounding effects of significant variables in the univariate analysis were assessed. The effect of the main opium consumption was calculated by adjusting the effect of the other possible risk factors (such as smoking). All statistical analyses were performed using Stata Software, version 11.0 (Stata Corp., College Station, TX, USA).

Results

We approached 174 cases and 348 healthy controls. Thirty two patients did not participate in the study; the frequency of non-response was 18.4 %. The frequencies of cancers were: gastric 62.7 %, liver: 13.4 %, pancreas 11.3 %, esophagus 10.5 %, and oral cavity 2.1 %. Around 73.2 % of cases were male (N = 104). Among cases, 69 patients (48.5 %) were in the 50 – 70 years old age-group. Over 50 % of cases were illiterate or low-literate. The controls were well matched to their cases by age and sex, and no statistically significant difference was found (all p-values were $>$ 0.05), (Table 1).

Table 2 shows the results of opium consumptions, smoking and alcohol use. As shown in this table, 38 % of subjects in "all cancers" subgroup had the history of opium use, while it was only 8.5 % in their controls. It means that the opium use had an adjusted

Table 1. Demographic information of cases and controls

Variables	Matched controls	All UGI cancers*	Matched controls	Gastric cancer**	Matched controls	Other UGI cancers***
N	284	142	178	89	106	53
Mean (SD)	62.4 (12.3)	61.9 (12.7)	63.2 (11.6)	62.7 (12.1)	61.0 (13.4)	60.6 (13.7)
Gender						
Male	208 (73.2 %)	104 (73.2 %)	138 (77.5 %)	69 (77.5 %)	70 (66.0 %)	35 (66.0 %)
Female	76 (26.8 %)	38 (26.8 %)	40 (22.5 %)	20 (22.5 %)	36 (34.0 %)	18 (34.0 %)
P-value	0.9		0.9		0.9	
Marital status						
Married	282 (99.3 %)	139 (98.0 %)	178 (100.0 %)	88 (99.0 %)	104 (98.0 %)	51 (96.0 %)
Single	2 (0.7 %)	3 (2.0 %)	0 (0.0 %)	1 (1.0 %)	2 (2.0 %)	2 (4.0 %)
P-value	0.2		0.1		0.6	
Age						
≤ 50	42 (15.0 %)	28 (20.0 %)	24 (13.5 %)	17 (19.1 %)	18 (17.0 %)	11 (21.0 %)
51–70	165 (58.0 %)	69 (48.5 %)	104 (58.5 %)	43 (48.3 %)	61 (57.5 %)	26 (49.0 %)
> 70	77 (27.0 %)	45 (31.5 %)	50 (28.0 %)	29 (32.6 %)	27 (25.5 %)	16 (30.0 %)
P-value	0.6		0.8		0.6	
Education						
Illiterate & elementary	181 (63.7 %)	96 (67.6 %)	112 (63.0 %)	60 (67.3 %)	69 (65.0 %)	36 (68.0 %)
Middle & high school	70 (24.7 %)	39 (27.4 %)	44 (24.7 %)	22 (24.7 %)	26 (25.0 %)	17 (32.0 %)
Diploma & above	33 (11.6 %)	7 (5.0 %)	22 (12.3 %)	7 (8.0 %)	11 (10.0 %)	0 (0.0 %)
P-value	0.03		0.1		0.1	

*Includes all upper gastrointestinal cancers (oral cavity, stomach, oesophagus, liver and pancreas); **Only includes gastric cancer; ***Includes other upper gastrointestinal cancers (oral cavity, oesophagus, liver and pancreas).

OR of 4.0 (95 % CI: 2.2 – 7.0). The adjusted OR for gastric cancer was 3.0 (95 % CI: 1.6 – 5.6). Similarly, the corresponding OR for the other cancers was 9.3 (95 % CI: 1.6 – 53.9).

Our findings showed that, the amount of daily use of opium increased the risk of all UGI cancers and gastric, with adjusted ORs of 14.0 (95% CI: 4.7 – 47.5), and 13.0 (95 % CI: 4.2 – 41.9), respectively. Furthermore, the duration of opium use significantly increased the risk in all UGI cancers and gastric, (adjusted ORs 12.0, 95 % CI: 3.2 – 44.1, and 10.5, 95 % CI: 2.4 – 46.1 respectively). Moreover, in all UGI cancer subjects, current user were at higher risk of UGI cancer than those who had a history of opium use. Cumulative consumption of opium with an adjusted OR of 18.7 (95 % CI: 5.5 – 63.3) had a strong correlation with the risk of all UGI cancers; which reflects the presence of a dose-response relationship between opium consumption and the incidence of all UGI cancers. Furthermore, this dose-response association was also observed for gastric cancer (adjusted OR 9.2; 95 % CI: 2.5 – 33.7).

Around 44 % of the cases were cigarette smokers, whereas this frequency was 22.2 % among controls. Although ever cigarette smoking was associated with an increased risk of all UGI cancers; OR = 4.5 (95 % CI: 2.5 – 8.2) in the univariate analysis; it was not significant after adjusting for diet and opium use; OR = 1.8 (95 % CI: 0.8 – 3.9). Moreover, for the gastric cancer, the association obtained in the multivariate analysis was not significant either; OR = 1.4 (95 % CI: 0.8 – 2.3). However, the adjusted OR was significant for the other UGI cancers; OR = 5.5 (95 % CI: 2.0 – 14.7).

The cumulative consumption of cigarettes increased the risk of all UGI cancers in univariate analysis; OR = 6.1 (95 % CI: 3.0 – 12.0), but after adjustment for potential confounding variables such as diet, again the OR decreased to 2.6 (95 % CI: 1.0 – 6.5). Similarly, for gastric cancer, the adjusted OR was 2.4 (95% CI: 0.8 – 7.2); and for the other cancers was 8.6 (95 % CI: 1.3 – 56.8).

Only 4.0 % of the participants had a history of alcohol use. In the all UGI cancers, 5.6 % of cases and 3.2 % of the controls had a record of alcohol use. The OR obtained for all cases was not significant in the multivariate analysis; OR = 1.8 (95 % CI: 0.3 – 8.1). Similarly, for the gastric cancer and for the other cancers

the adjusted ORs were 1.2 (95 % CI: 0.3 – 4.4) and 1.2 (95 % CI: 0.6 – 3.5) respectively.

Discussion

This study aimed to assess the association between opium use and the risk of UGI cancers. According to the results of this study, consumption of opium may increase the risk of these cancers. In this study, a dose-response relationship was also observed between opium use and the risk of UGI cancers. These associations also observed for gastric cancer separately.

The observed association between opium use and UGI cancers was strong and compatible with the findings in some other studies which might support a causal relationship.^{10–17} The strength of the association achieved in this study was relatively high and opium use increased odds of all cancers four times, it was three times for gastric cancer and nine times for other UGI cancers. It is worth mentioning that after adjusting for the other possible confounding factors such as smoking, alcohol use and diet, this association was still significant and strong.

Compatible with our findings, in other studies carried out in the north of Iran on the association between opium and gastric and esophageal cancers, a significant and strong association was observed. Moreover, they found a dose-response relationship.^{14–17} In addition, many studies have also shown that opium use may increase the risk of some malignancies such as gastric,^{16,17} esophageal,^{14,15} larynx,¹² bladder^{10,11} and lung¹³ cancers, also may increase the mortality resulting from these cancers.²² These studies all emphasized the possible carcinogenic effects of opioids.

Numerous mechanisms have been proposed regarding the association between opium use and cancer. Using opium and its alkaloids such as morphine may have mutagenic effects.²³ Empirical studies have shown that opium pyrolysis products have mutagenic effects on salmonella strains.²⁴ Also, morphine pyrolysis products and alkaloids have caused sister chromatid changes in human lymphocytes and morphological changes in cultured Syrian hamster embryo cells.²⁵ It was also observed that after these drugs were injected in local tissue, subdermally, intratracheal and into the

Table 2. The ORs between upper gastrointestinal cancers and using opioid derivatives, cigarette and alcohol

Variables	ALL UGI cancers				Gastric cancer			
	Cases (N %)	Controls (N %)	Unadjusted OR (95%CI)	adjusted* OR (95%CI)	Cases (N %)	Controls (N %)	Unadjusted OR (95%CI)	adjusted OR (95%CI)
Opium use								
never	88 (62.0 %)	260 (91.5 %)	Referent	Referent	55 (61.8 %)	161 (91.5 %)	Referent	Referent
ever	54(38.0 %)	24 (8.5 %)	4.9 (2.9–8.4)	4.0 (2.2–7.0)	34 (38.2 %)	17 (9.5 %)	3.9(2.9–6.8)	3.0 (1.6–5.6)
Amount of daily use								
Never used	88 (62.0)	259 (91.0)	Referent	Referent	55 (8.61)	161 (90.5)	Referent	Referent
≤ median**	11 (8.0)	13 (5.0)	7.4 (2.3–23.8)	7.1 (6.1–31.9)	6 (7.0)	7 (4.0)	6.0 (1.4–25.2)	5.5 (1.0–28.4)
>median	42 (30.0)	12 (4.0)	22.2 (7.9–62.1)	14.0 (4.7–47.5)	28 (31.2)	10 (5.5)	15.2(4.9–47.3)	13.0 (4.2–41.9)
Duration								
Never used	88 (62.0)	259 (91.0)	Referent	Referent	55 (61.8)	161 (90.5)	Referent	Referent
≤ median	29 (20.5)	14 (5.0)	14.0 (4.9–39.8)	10.1 (3.2–31.6)	21 (23.6)	10 (5.5)	9.7 (2.8–33.2)	6.8 (1.7–26.8)
>median	25 (17.5)	11 (4.0)	18.5 (6.0–56.9)	12.0 (3.2–44.1)	13 (14.6)	7 (4.0)	15.4 (4.3–54.7)	10.5 (2.4–46.1)
Cumulative use of Opium**								
Never used	88 (62.0 %)	260 (91.5 %)	Referent	Referent	55 (61.8 %)	161 (90.5 %)	Referent	Referent
≤ Median	12 (8.5 %)	13 (4.5 %)	7.1 (2.2–23.2)	5 (1.1–22.4)	8 (9.0 %)	8 (4.5 %)	7.3 (1.8–28.8)	7.3 (1.2–43.0)
> Median	42 (29.5 %)	11 (4.0 %)	23.6 (8.2–68.5)	18.7 (5.5–63.3)	26 (29.2 %)	9 (5.0 %)	15.2 (4.8–47.8)	9.2 (2.5–33.7)
Cigarette smoking								
Never	79 (56.0 %)	221 (77.8 %)	Referent	Referent	47 (53.0 %)	130 (73.0 %)	Referent	Referent
Ever	63 (44.0 %)	63 (22.2 %)	4.5 (2.5–8.2)	1.8 (0.8–3.9)	42 (47.0 %)	48 (27.0 %)	2.3(1.5–3.5)	1.4 (0.8–2.3)
Amount of daily use								
Never used	79 (56.0)	221 (77.8)	Referent	Referent	47 (52.8)	130 (73.0)	Referent	Referent
≤ median**	25 (17.0)	32 (11.2)	3.3 (1.6–6.8)	1.3(0.4–3.5)	15 (17.0)	23(13.0)	2.4 (1.0–5.8)	0.8 (0.2–2.8)
>median	38 (27.0)	31 (11.0)	6.0 (2.9–12.1)	2.4(1.0–6.0)	27 (30.2)	25 (14.0)	5.1 (2.2–11.8)	1.9 (0.7–5.2)
Duration								
Never used	79 (56.0)	221 (77.8)	Referent	Referent	47 (52.8)	130 (73.0)	Referent	Referent
≤ median	45 (31.3)	37 (13.0)	5.4 (2.8–10.7)	2.1 (0.8–4.9)	28 (31.5)	25 (15.0)	4.5 (1.9–12.4)	1.5 (0.5–4.2)
>median	18 (12.7)	26 (9.2)	3.1 (1.3–7.1)	1.4 (0.4–4.4)	14 (15.7)	21 (12.0)	2.6 (1.0–6.7)	1.2 (0.3–4.2)
Cumulative use of cigarette smoking								
Never used	79 (55.6 %)	221 (77.8 %)	Referent	Referent	47 (52.8 %)	130 (73.0 %)	Referent	Referent
≤ Median***	23 (16.2 %)	31 (11.0 %)	3.1 (1.5–6.5)	1.0 (0.3–2.9)	13 (14.6 %)	22 (12.4 %)	2.2 (0.9–5.4)	1.0 (0.2–3.8)
> Median	40 (28.2 %)	32 (11.2 %)	6.1 (3.0–12.0)	2.6 (1.0–6.5)	26 (14.6 %)	26 (14.6 %)	5.3 (2.2–12.4)	2.4 (0.8–7.2)
Alcohol use								
Never use	134 (94.4 %)	275 (96.8 %)	Referent	Referent	85 (95.5 %)	172 (96.6 %)	Referent	Referent
Ever use	8 (5.6 %)	9 (3.2 %)	1.5 (0.5–4.6)	1.8 (0.3–8.1)	4 (4.5 %)	6 (3.4 %)	1.3 (0.6–2.7)	1.2 (0.3–4.4)

*Confounding effect of some specific dietary factors such as consumption of meat, fruit and vegetable, hydrogenated fats, and other key exposure (smoking) has been controlled; ** Median use in the control group was taken as the cut off point;*** Cumulative use was calculated by multiplying the average use (per day) by consumption period (in years).

gastrointestinal tract of mice, they caused carcinogenic changes.²³

It should be mentioned that, in order to obtain more profit, during the processing of these drugs in Iran, many impurities are being added; some of these substances might have poisonous effects. As the results of this impurity it was shown that the level of lead in a sample of opium and in the addicts' blood was high; inorganic lead may have severe toxicity and even carcinogenic effects.^{26–28} However, even with these consistent evidences we have to say that the carcinogenic mechanisms of opium have not been known well.

While smoking is one of the known risk factors of some of UGI cancers,^{29,30} the association between smoking and cancers did not reach a significant level in this study, which might be due to the small sample size. In some previous studies carried out in Iran, the association between smoking and gastric and esophageal cancers

did not reach a significant level either.^{14–16} Lower observed associations in Iran might be due to the amount and types of cigarettes used in Iran which could be different from the other parts of Iran.¹⁶ In fact, the average number of cigarettes used by controls was relatively low (12.3 packed-year). This result was consistent with the results obtained in a study carried out in Golestan; (13.5 packed-year).¹⁴

In two studies in Linxian (China), and in Golestan (Iran) (both with very high risk of esophageal cancer) it was shown that smoking was more prevalent in men than in women; however, the incidence of esophageal cancer in these two regions was the same in both sexes which shows the effect of some other important risk factors which might suppress the effect of smoking.³¹

Opioids are highly used in some regions of Iran. In an opium

study in Golestan, 17 % of participants used opioids;¹⁶ and some studies in Kerman have pointed to high consumption of opium as well.^{18,19} Based on these information and because of the strong association and also relatively high consumption rate, a considerable part of the burden of these cancers might be explained by opioids use. It is estimated that around 15 million opioids users are around the world;¹⁶ such a strong association between opium consumption and UGI cancers is a very important point of concern.

This study had some limitations. Separate study of UGI cancers was not possible like any case-control study because of small sample size. Our results are prone to interviewer and recall bias during data collection as well. In addition, the under-reporting of opium use, particularly in controls, is a potential bias; however, we standardized the method of interview, and a trained staff interviewed almost all subjects to minimize the impact of such a bias.

However, the most positive point of this study was the confirmed histopathological diagnosis of cancers which minimized the possibility of misclassification bias. Another good point was that our controls were all neighbors of cases which probably controlled the confounding effects of socioeconomic factors and environmental exposures.¹⁵ In addition, as an advantage, we used a questionnaire that had been validated in Iranian population.^{20,21}

In summary, there is a high incidence of gastrointestinal cancers in Iran as well as a high consumption of opium. In this study, a strong association was observed between opium use and the risk of gastrointestinal cancers which may explain some part of the high incidence of these cancers in at least some parts of Iran.

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