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Opium Use and Risk of Lower Gastrointestinal Cancers: Population-Based Case-Control Study in South of Iran

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Abstract

Background: Colorectal cancers, including colon, rectum and anus, are relatively prevalent in Iran. Use of opium and its derivatives is also considerably prevalent in some areas in Iran.
Objectives: The aim of this study was to assess the association between use of opium and its derivatives, and incidence of lower gastrointestinal (LGI) cancers.
Methods: This study was a matched case-control study in Shiraz (south of Iran). Cases were the new colorectal cancers from cancer registry center of Shiraz University of Medical Sciences and controls were selected from healthy volunteers of cases' neighbors matched for age and gender (2 controls per 1 case). Data related to consumption of opium and its derivatives, smoking, alcohol use and diet status were collected through a structured questionnaire. The conditional logistic regression models were used to assess all associations.
Results: 160 cases and 320 controls participated in the present study with non-response rate less than 9 %. Opium use was associated with increased risk of colorectal cancer (adjusted OR = 4.4; 95% CI: 2.2 - 8.8). Also, a dose-response association was observed between cumulative consumption of opium and the colorectal cancer incidence (OR = 3.8; 95% CI: 1.5 - 9.1), and (OR = 4.6; 95% CI: 1.7 - 12.0) for low and high use, respectively. Also, the significant dose-response association was observed for low (OR = 3.4; 95% CI: 1.2 - 9.2) and high (OR = 7.7; 95% CI: 1.5 - 38.6) opium use with presence of colon cancer.
Conclusions: The results of this study showed that opium use can be an important risk factor for colorectal cancer in Iran.

Keywords: Risk Factor, Colorectal Cancer, Opium, Case-Control

1. Background

Nowadays, cancer is one of the major health problems in the world and the importance of this problem is increasing in Iran (1). Colorectal cancer is one of the major cancers in the world (2). Colorectal cancers (including colon, rectum and anus) are the most common type of gastrointestinal tract cancer and allocate the third rank in men and fourth rank in women in Iran (1, 3, 4). The annual incidence of this cancer is more than 134,000 new cases and 55,000 deaths are reported annually due to colorectal cancer. Also, 10 percent of deaths due to cancers in America are related to this cancer (1, 5). During the recent years, studies in Iran have shown that more than 60 percent of cancer deaths are due to digestive cancers, especially colorectal cancers (6). Although the incidence of colorectal cancers have a lower risk in all age groups of Iranian population than other developing countries, the incidence of colon cancer has been developing at an alarming rate during the last 25 years (7-9). According to the reports, cancer incidence rates have increased 5% in women and 17% in men (10).

Since more than 90% of cases of this disease are already diagnosed in adults over the age of 55 years, most of these people are considered as target populations in screening programs (11). In the same vein, recent studies in Iran showed that the incidence of these cancers in younger

people is increasing so that the incidence rates in an Iranian less than 40 years is almost 5 times that of the rest of the world (6, 10, 12, 13). This emphasizes major changes in lifestyle and the accuracy of forecasting studies on growing trends of colorectal cancer in active people of community (8).

The geographical distribution of colorectal cancer is very different and its dependent on various environmental and behavioral factors (8, 12, 14). The results of a study in Fars province showed that the annual incidence rate of colorectal cancer for men and women was 8.61 and 10.47 per 100,000 persons, respectively. Also, the annual colon cancer mortality for men and women was 1.54 and 2.46 per 100,000 persons, respectively. Moreover, the mortality rates for colon cancer in the other studies from southern parts of Iran were reported 0.41 and 0.34 per 100,000 persons (1, 4, 15).

Previous studies have verified the association between some risk factors such as obesity (16) inactivity (16) low socioeconomic status (16, 17), smoking (18), some nutritional habits such as carbohydrates, fats, red meat and low fiber use (19, 20) with colorectal cancer. Also the effects of alcohol consumption on colorectal cancer have been confirmed by some studies, while other studies have rejected this effect (21). Use of opium and its derivatives has also been questioned as a factor (22). However, it has been proved as a risk factor for various cancers such as gastric (23, 24), lung (25), larynx (26), bladder (27), and esophagus (24). Also, in a study in north of Iran, it was demonstrated that the level of morphine metabolites in the urine sample of patients in high risk regions for esophageal cancer was 6 times higher than in other regions (28). Although studies indicate high opium use in the world (29, 30) and forecasts show that opium use is increasing by 8% annually in Iran (31), It seems that only one study shows the relationship between the use of opium and derivatives with colorectal cancers (32).

The high consumption of opium in Iran is probably due to drugs transportation from Afghanistan as the most important opium producer in the world which resulted in availability of opium in Iran, especially in Fars province in south of Iran.

2. Objectives

This case-control study was done to investigate the possible association between opium use and the incidence of colorectal cancer in Fars province as a major area of drug transportation with high incidence rate of colorectal cancers.

3. Methods

3.1. Sample of the Study

New cases diagnosed between Jan. 214 to Dec. 2015 from cancer registry center of Shiraz University of Medical Sciences were included in this matched case-control study. They participated in this study based on pathology based information and hospital based information. Matched controls were selected for each case in terms of age and sex from cases' neighbors. The following assumptions were used to calculate the sample size: the minimum desired odds ratio of 2, the numbers of control per case ratio of 2: 1, the prevalence of opium derivatives use in the general population 0.2 and the statistical power and the alpha error 0.8 and 0.05, respectively. The minimum sample size of 175 was calculated based on these assumptions.

At the first step, the time and date of the interview was determined through a phone call to the cases or their families. In order to reduce the non-response cases, we referred to patients' address if the coordinating with patients was not possible by phone call. For every subject, two neighbor controls were selected at the nearest from the right side of the case's house matched in terms of age ($\pm$ 5) and gender. Controls had to meet inclusion criteria and informed consent was acquired to participate in the study. The protocol of our study was approved by ethics committee of Larestan University of Medical Sciences by registry number 1393,171.

3.2. Tools and Data Collection Procedure

Data were collected through a questionnaire which consisted of three parts. The first part included demographic information such as age, gender, marital status and education; the second part asked the dietary information's and the third part focused on history of opium and its derivatives, smoking and alcohol use information. The validity and reliability of this questionnaire was verified in the previous study (33). Two interviewers conducted an interview to avoid the interpersonal bias. Also interviewers were trained the required practical training to communicate appropriately in a friendly and relaxed environment to decrease the under reporting problem in the control group. Control group answered the questions related to opium and tobacco use at the end of the interview. In order to quantify the consumption level of opium and smoking, questions were asked about the history of previous and present consumption. Also the cumulative lifetime use was calculated based on the frequency and duration of use in different ages in order to consider the probable use fluctuation during different periods. Daily opium use was measured based on "Nokhod" as a local measurement unit that is equal to 0.2 grams.

Types of substances were divided into 4 categories as follows: raw opium, sukhte (burned opium), shireh (opium sap) and heroin. Since heroin and burned opium were not used, just raw opium and opium sap were considered as an aggregative in final analysis. Dietary questions include Iranian eating habit questions for the last 10 years period before the interview were used to assess the dietary status.

This study was approved by the ethical committee of Larestan faculty of medical sciences. Interviewers tried to explain the study purpose in detail to take verbal informed consent before the interview.

3.3. Data Analyses

Cumulative consumption for smoking and opium use was calculated by average daily use multiplied by the duration of use. Finally participants of the study were divided in to 3 sub-groups of never use, low use ($\leq$ median use in the controls) and high use ($>$ median use in control group). Current users are those who used opium and smoked during this study. Alcohol used had a low prevalence so that the analysis of the effects of alcohol was divided into never use and ever use. The conditional logistic regression analysis was used to investigate the association between opium use, smoking, and alcohol use with colorectal and colon cancers, respectively. In multivariate model, all variables with p value less than 1.0 were inserted in the model. The stata 12.0 software were used for all computations.

4. Results

A number of 160 cases and 320 controls participated in this study and the non-response rate was less than 9 %. Of 160 eligible cases that had participated in this study, 55.63 % were men and 87.5 % of them were married. Also, 48.13% of cases were 51 - 70 years-old and 18.75% were over 70 years old. Moreover, the frequencies of colon, rectum and anus cancers were 58.2%, 30% and 11.8%, respectively.

Other cases and controls' demographic information is shown in Table 1. The mean years of opium use were 30.33 $\pm$ 16.28 and the most common initial user cases were 20 to 30 years old. Generally 20 % of cases and 5 % of controls used opium previously ($P < 0.001$).

Multivariate conditional logistic regression analysis was used to identify the association between use of opium, smoking and alcohol with colorectal and colon cancer.

The results of this analysis showed that there is a significant association between opium use with colorectal (OR: 4.48 CI; 2.27 - 8.82) and colon cancer (adjusted OR: 5.4 CI; 2.19 - 13.55). Also, daily use of opium was significantly associated with increasing the risk of colorectal (OR: 6.53 CI; 1.75 - 24.41) and colon cancer (OR: 7.11 CI; 1.78 - 28.39). Moreover, duration of opium use was significantly associated with increase the risk of colorectal (OR: 5.83 95 % CI: 2.23 - 15.21) and colon cancer (OR: 7.2, 95 % CI: 1.87 - 28.26). Therefore, cumulative consumption of opium and its derivatives with an adjusted odds ratio of 4.63(95 % CI: 1.78 - 12.05) have a strong association with increased risk of colorectal cancer and suggest the presence of a dose-response relationship between opium use and the incidence of all colorectal cancers. Also, this dose-response relationship was observed in colon cancer groups (OR: 11.66; 95 % CI: 1.57 - 24.92).

The multivariate analysis in colorectal cancer groups showed that smoking was not significantly associated with an increased risk of cancer (OR 1.01; 95 % CI: 0.59 -1.78). The obtained odds ratio in multivariate analysis of colon cancer does not have a significant relationship (OR: 1.46; 95 % CI: 0.71 - 3.01). Findings have shown that daily use of smoking does not have any statistical relationship in colorectal cancer groups (OR: 1.06; 95 % CI: 0.54 - 2.08) also the obtained odds ratio in multivariate analysis of colon cancer groups was not significant (OR: 1.8; 95 % CI: 0.8 - 3.7) (Table 2).

In addition, no significant statistical relationship was found between smoking duration and the risk of colorectal cancers (OR: 1.1; 95 % CI: 0.66 - 2.11) and colon cancer (OR: 2.55; 95 % CI: 0.96 - 6.60). There was not observed any significant association in multivariate analysis of cumulative smoking in colorectal cancer (OR: 1.12; 95 % CI: 0.47 - 1.89). In the same vein, an adjusted odds ratio of cumulative smoking use was not significant in colon cancer (OR: 1.52; 95 % CI: 0.62 - 3.74). About 10 % of participants of this study use alcohol. This amount was almost equally in control and case groups for colorectal cancer. Odds ratio was not significant in the multivariate analysis of this sub-group (OR: 1.07; 95 % CI: 0.51 - 2.11). Similarity, odds ratio was not significant in the multivariate analysis of colon cancer sub-group (OR: 1.7; 95 % CI: 0.64 - 4.82) (Table 2).

5. Discussion

The aim of this study was to assess the association between opium use and the risk of colorectal cancers. Findings of this study indicate that consumption of opium and its derivatives may increase the risk of colorectal cancers which include colon, rectum, and anus. Also, a dose-response relationship was observed between opium use and colorectal cancers.

After adjustment for the possible confounding variables such as eating fruit, vegetable, meat and oils, the observed association between opium use and colorectal cancers was relatively strong (adjusted OR 4.48 and 5.4 for colorectal and colon cancer respectively) which might sup-

Table 1. Demographic Information and Case-Control Group

Variable	Matched Controls	CRC Cancers[a]	Matched Controls	Colon Cancer[b]
N	320	160	186	93
Gender				
Male	178 (55.63)	89 (55.63)	112 (60.22)	56 (60.22)
Female	142 (44.38)	71 (44.38)	74 (39.78)	37 (39.78)
P value	0.99		0.99	
Marital status				
Married	268 (83.75)	140 (87.50)	163 (87.63)	83 (89.25)
Single	52 (16.25)	20 (12.50)	23 (12.37)	10 (10.75)
P value	0.27		0.70	
Age				
$\leq$ 50	101 (31.56)	53 (33.13)	73 (39.25)	38 (40.86)
51 - 70	149 (46.56)	77(48.13)	81 (43.55)	39 (41.94)
> 70	70 (21.88)	30 (18.75)	32 (17.20)	16 (32.4)
P value	0.70		0.97	
Education				
Illiterate and elementary	100 (31.25)	44 (27.50)	55 (29.57)	24 (25.81)
Middle and high school	40 (12.50)	15 (9.38)	24 (12.90)	9 (9.68)
Diploma and above	180 (56.25)	101 (63.13)	107 (57.53)	64 (64.52)
P value	0.32		0.51	

[a] It includes colon, rectum and anus.
[b] It contains only colon cancer.

port a causal association. The results of this study were consistent with some other studies that reported the significant association between opium consumption with gastrointestinal tract cancers, especially with upper gastrointestinal cancers such as esophagus and gastric cancer (24, 34). Also, some studies reported that the risk of colorectal cancer is high in patients with esophageal cancer (35). The common risk factors for colorectal and esophageal cancer may play an important role in this comorbidity, so the findings of this study show that opium consumption relatively increases the risk of colorectal cancers as much as esophageal cancer in opium users.

There are a lot of biochemical and physiological mechanism for relationship between opium consumption and risk of cancer (36, 37). Studies have shown that opium pyrolysis and it alkaloids like morphine can result in mutagenicity, morphological changes and exchange sister chromatid in human lymphocytes (38). Also, the laboratory animals studies have shown that the injection into the animal digestive tract cause the neoplasms changes in their tissues (36). Moreover, studies have shown that the non-organic lead that is added to the opium drugs during opium processing could be carcinogen. Previous studies on opium consumers showed that the serum level of opium in this group was higher than normal status (9, 39).

Although smoking was reported as a risk factor for colorectal cancers in several studies (16, 18, 40), this study showed no significant relationship between smoking and colorectal cancers. Some limitations such as under-reporting of smoking use, different smoking pattern in different region and also small sample size in this study are considered as explanations for this matter.

In addition, there is no relationship between alcohol use and colorectal cancer in this study and it is consistent with the findings of other studies (41, 42). Cho and colleagues have shown that low alcohol consumption with low risk and high use would increase the risk but overally there was no significant differences between alcohol consumption and risk of colorectal cancer (21). But the risk of colorectal cancer had increased due to alcohol use by 72% and 30% in China and America, respectively (43, 44). The under reporting of alcohol consumption due to illegal alcohol use in some Islamic countries such as Iran may be considered as a justification for such inconsistencies.

The effect of diet on the relationship between opium and its derivatives use, and the risk of colorectal cancer were investigated in this study. Findings of this study are consistent with other studies that show fruit and vegetables use play a protective effects on colorectal cancer. However, a direct association was found between low consumption of fiber, high consumption of fatty foods and red meat with colorectal cancer (7, 19, 20, 45, 46).

The results of this study are prone to some biases as other case-control studies such as recall bias and inter-

Table 2. The Association Between the Opium and its Derivatives, Smoking and Alcohol Use with the Colorectal Cancers[a]

Variable	CRCs				Colon Cancer			
Opium	Cases	Controls	Unadjusted OR (95%CI)	Adjusted[b] OR (95%CI)	Cases	Controls	Unadjusted OR (95%CI)	Adjusted[b] OR (95%CI)
Opium use								
Never	128 (80.00)	304 (95.00)	Referent	Referent	75 (80.65)	177 (95.16)	Reference	Reference
Ever	32 (20.00)	16 (5.00)	4.37 (2.33 - 8.22)	4.48 (2.27 - 8.82)	18 (19.35)	9 (4.84)	4.94 (11.88 - 2.06)	5.4 (2.19 -13.55)
Daily use of opium								
Never used	128 (80.00)	304 (95.00)	Referent	Referent	75 (80.65)	177 (95.16)	Reference	Reference
≤ Median[c]	22 (13.75)	13 (4.06)	3.94 (1.88 - 8.22)	3.76 (1.71 - 8.23)	9 (9.68)	5 (2.69)	3.90 (1.29 - 11.7)	2.0 (0.82 - 8.30)
> Median	10 (6.25)	3 (0.94)	7.24 (1.98 - 26.62)	6.53 (1.75 - 24.41)	9 (9.68)	4 (2.15)	4.86 (1.48 - 15.97)	7.11 (1.78 - 28.39)
Duration of opium use								
Never used	128 (80.00)	304 (95.00)	Referent	Referent	75 (80.65)	177 (95.16)	Reference	Reference
≤ Median	15 (9.38)	10 (3.13)	3.15 (1.40 - 7.06)	2.58 (1.11 - 6.02)	7 (7.53)	5 (2.69)	3.10 (1.79 - 11.82)	2.67 (1.91 - 8.26)
> Median	17 (10.36)	6 (1.88)	5.87 (2.30 - 14.95)	5.83 (2.23 - 15.21)	11 (11.83)	4 (2.15)	4.86 (1.78 - 14.87)	7.2 (1.87 - 28.26)
Cumulative opium use[d]								
Never used	128 (80.00)	304 (95.00)	Referent	Referent	75 (80.65)	177 (95.16)	Reference	Reference
≤ Median[c]	16 (10.00)	10 (3.13)	3.20 (1.45 - 7.05)	3.82 (1.58- 9.18)	11 (11.83)	7 (3.76)	3.14 (1.21 - 8.10)	3.40 (1.25 - 9.26)
> Median	16 (10.00)	6 (1.88)	5.33 (2.08 - 13.62)	4.63 (1.78 - 12.05)	7 (7.53)	2 (1.08)	7.02 (1.45 - 33.69)	7.71 (1.54 - 38.64)
Cigarette smoking								
Never	118 (73.75)	243 (75.94)	Referent	Referent	66 (70.97)	142 (76.34)	Reference	Reference
Ever	42 (26.25)	77 (24.06)	1.14 (0.71 - 1.84)	1.01 (0.59 - 1.78)	27 (29.03)	44 (23.66)	1.44 (0.75 - 2.7)	1.46 (0.71 - 3.01)
Daily use of tobacco								
Never used	118 (73.75)	243 (75.94)	Referent	Referent	66 (70.97)	142 (76.34)	Reference	Reference
≤ Median[c]	20 (12.50)	42 (13.13)	1.00 (0.55 - 1.81)	1.02 (0.52 - 1.99)	13 (13.98)	21 (11.29)	1.2 (0.7 - 2.2)	1.6 (0.5 - 3.6)
> Median	22 (13.75)	35 (10.94)	1.35 (0.71 - 2.54)	1.06 (0.54 - 2.08)	14 (15.05)	23 (12.37)	1.3 (0.7 - 2.6)	1.8 (0.8 - 3.7)
Duration								
Never used	118 (73.75)	243 (75.94)	Referent	Referent	66 (70.97)	142 (76.34)	Reference	Reference
≤ Median[c]	25 (15.63)	42 (13.13)	1.06 (0.58 - 1.9)	1.03 (0.57 - 2.03)	13 (13.98)	29 (15.60)	1.04 (0.47 - 2.30)	1.30 (0.54 - 3.11)
> Median	17 (10.63)	35 (10.94)	1.27 (0.68- 2.39)	1.1 (0.66 - 2.11)	14 (15.05)	15 (8.06)	2.3 (0.94 - 5.69)	2.55 (0.96 - 6.60)
Cumulative smoking[d]								
Never used	118 (73.75)	243 (75.94)	Referent	Referent	66 (70.97)	142 (76.34)	Reference	Reference
≤ Median[c]	22 (13.75)	43 (13.44)	1.09 (0.60 - 1.97)	1.09 (0.40 - 1.87)	13 (13.98)	25 (13.44)	1.23 (0.57 - 2.67)	1.47 (0.63 - 3.43)
> Median	20 (12.50)	34 (10.63)	1.25 (0.66 - 2.36)	1.12 (0.47 - 1.89)	14 (15.04)	19 (10.22)	1.71 (0.76 - 3.86)	1.52 (0.62 - 3.74)
Alcohol use								
Never use	144 (90.00)	289 (90.31)	Referent	Referent	83 (89.25)	168 (90.32)	Reference	Reference
Ever use	16 (10.00)	31 (9.69)	1.04 (0.53 - 2.03)	1.07 (0.51 - 2.11)	10 (10.75)	18 (9.68)	1.15 (0.46 - 2.83)	1.7 (0.64 - 4.82)

[a] Values are expressed as No. (%).
[b] The confounding effects of some special dietary factors such as use of meat, fruit, vegetables hydrogenated fats and other main exposure (smoking) are controlled.
[c] Median consider as standard for high and low use in standard group.
[d] Cumulative consumption was calculated through multiplying consumed amount (daily) to period of use (yearly).

viewer bias. Also, the under-reporting of opium consumption, especially in control groups is a potential bias. However, we tried to minimize the interviewer bias by training interviewers, standardizing the method of interview and using experienced interviewers. However, the present study has some strengths. For example, cases were confirmed based on histopathological diagnosis history to prevent the misclassification bias. Also, population based neighbor control was used to control the confounding effects of socioeconomic factors, exposure to the environmental risk factors and other potential unknown confounders that may confound the associations (47). Moreover, as an advantage, the validity and reliability of the questionnaire in this study were verified for Iranian population (33).

The mean age of the patients in this study showed that the colorectal cancers occurred after middle-ages in Fars province. However, the youngest patients in lower range of age distribution in this study showed that the age of onset in colorectal cancer decreased in south of Iran. The higher prevalence of some risk factors in the younger age groups includes the consumption of opium and their derivatives may be potential reasons for this change in age pattern of colorectal cancers.

In conclusion, the results of this study indicated that there was a strong association between opium use and the risk of lower gastrointestinal cancers which may explain the high prevalence of opium use in south of Iran as well as high incidence of lower gastrointestinal cancers. Moreover, the opium users can be considered as one of the target groups for screening, early detection and treatment programs for gastrointestinal cancers.

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Footnotes

Authors' Contribution: Kamran B Lankarani designed the study, analyzed the data and wrote the paper. Zahra Khosravizadegan, Ahmad Naghibzadeh Tahami and Mojtaba Akbari contributed to study design and analysis. Mahmoud Khodadost and Behnam Honarvar contributed to the data cleaning and literature review. Behnam Khodadost, Forough Goodarzi, Kimia Jokari, Maryam Akbari contributed to the data collection, data linkage and writing-up process. Eghbal Sekhavati and Reza Tabrizi designed the study, analyzed the data and wrote the paper. All authors read and approved the final manuscript.

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