Can Opium Use Contribute to a Higher Risk of Colorectal Cancers? A Matched Case-control Study in Iran

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Abstract

Background: Colorectal cancers (CRCs) including colon, rectum and anal cancers are the third most prevalent cancers in the world. There are strong evidence showing the risk of the cigarette smoking, alcohol use, low physical activity and some types of diets in CRCs; however, few studies explored the relationship between opium use and CRCs. This study aimed to investigate the association between opioid use and the incidence of CRCs.

Methods: In a population-based matched case-control study in Kerman, Iran, 175 patients with colorectal cancers and 350 healthy controls (matched for age, sex, and place of residence) were interviewed from Sep 2014 to Nov 2014. Opium and its derivatives, cigarette, alcohol, and diet use were collected using a valid and reliable questionnaire. Conditional logistic regression was used to estimate odds ratios with 95% confidence intervals.

Results: The use of opioids was associated with an increased risk of CRCs (adjusted odds ratio= 4. 5, 95% CI: 2. 4-8. 7). In addition, a dose-response relationship was observed between the cumulative use of opioids and the incidence of CRCs (with low use OR=3. 7; 95% CI: 1. 5-8. 6 and high use OR= 8. 0; 95% CI: 2. 9-21. 7). This dose-response relationship was also strong in patients with colon cancers, with OR= 3. 9 (95% CI: 1. 5-9. 9) and 9. 4 (95% CI: 3. 3-27. 0) for the low and high uses of opioids, respectively.

Conclusion: Opioid use can lead to an increased risk of CRCs. Therefore, it is necessary to implement preventive policies to control the use of opioids.

Keywords: Risk factor, Colorectal cancers, Opioid, Case-control, Iran

Introduction

Colorectal cancers (CRCs) including colon, rectum and anal cancers are the third most prevalent cancers in the world (1). The incidence of these types of cancers has a vast geographical diversity, so that these cancers are among the first three cancers in the world and include 8 percent of all deaths attributable to cancer annually (2). More than 60% of deaths from cancer can be attributed to gastrointestinal cancers such as the CRCs in Iran (3-4). These cancers have had a considerable increase in developing countries including Iran, despite their low incidence in recent years compared with developed countries (5-7). It is the third most common in Iranian men after gastric and prostate cancers. Recently, these cancers have increased 5% in women and 17% in men (8 -9). In addition, these cancers occur at an earlier age than ever before and the incidence in the age groups less than 40 yr is almost five times the rest of the world that indicates the differences in risk factors among the younger age in Iran compared to developed countries (3-4, 9-10).

Although Iran is among the countries where the incidence of CRCs in all age groups is lower than the other parts of the world, but colon cancer has had the highest increase in recent years (11). In 2013, the results of a study in Kerman Province showed that CRCs had an increasing trend and it is predicted that the annual incidence of these cancers will increase 6% in the province by 2016 (12). In addition, in Kerman Province the age-specific incidence of these cancers in both genders is rated fourth among all cancers (13). These cancers occur in all racial and ethnic groups with an evident geographicaland age diversity (14)which shows the significant impact of environmental and behavioral factors on the incidence of these cancers (3, 6, 14). Previous studies have proved the relationship between some risk factors such as the high use of red meat (15-16), obesity (17), smoking (18), low physical activity (17) and low socioeconomic status and the incidence of these cancers (19).

One of the risk factors associated with various cancers questioned by researchers is the use of opium and its derivatives. The use of opium and its derivatives increased the risk of upper gastrointestinal, gastric, and bladder cancers 4. 0, 3. 0 and 3. 9 times (20-21). In addition, other studies have proved the use of opium and its derivatives as a risk factor for the cancers of the larynx (22), lungs (23), stomach (20, 24-25), bladder (21, 26-27), oral cavity (28) and esophagus (29-30). Despite this evidence, no certain study was found about the association between these cancers and the use of opioids especially opium, despite its widespread use in Iran and around the world (31-33). Evidence from previous studies refer to the high prevalence of drug use in some areas in the world (24, 33) and Iran particularly Kerman as one of the prevalent areas in Iran (32-34). In addition, morphine metabolites in the urine of residents in esophageal cancer high-risk areas in the north of Iran are 6 times higher than the low-risk areas (35).

There is a high incidence of opioid use with high impurities and additives in Iran (36-37). In addition, there is a high incidence of gastrointestinal cancers especially in the north of Kerman province (13), as well as the growing trend of CRCs in Iran, especially in Kerman province (12, 38). The present case-control study was conducted to investigate the relationship between the use of opioids and the incidence of CRCs in Kerman City.

Methods

Sample

In this matched case-control study, the incidence cases were extracted from the Cancer Registry of Kerman University of Medical Sciences, Deputy of Health, during Jan 2012 to Dec 2014. The incidence cases were diagnosed based on pathological and clinical data. For each case, two controls

were matched for age and sex from the neighbors.

The sample size was estimated 175 incidence cases based on the odds ratio of at least 2. 0, the control to case ratio of 2 to 1, the minimum exposure to opioid derivatives in the general population 20%, and the study power of 0. 8. After a phone call to the subjects and their families, a specific date and time was set for an interview. In order to reduce non-response, when people did not cooperate via phone calls, they were visited in person. Matching was based on two criteria including sex and age (±5). The nearest and first neighbor on the right side of the case home who had the inclusion criteria and willingness to cooperate in the study was selectedas the matched control. If the control was not home or did not want to cooperate, the next neighbor was approached. In addition, oral informed consent was taken before the interviews.

Tools and methods of data collection

Data were collected using a questionnaire consisting of three parts: a) demographic information including gender, age, education level and marital status; b) questions related to diet as confounding factors; c) information on the amount and use of opium and its derivatives, alcohol use and smoking. The validity and reliability of the questionnaire had been approved in a previousstudy (39). In order to minimize bias; all interviews were conducted by two trained interviewers. In order to better quantify opium and cigarette use the current and past exposure status was asked. The cumulative life time use of opioids based on the amount and duration of use in different ages was calculated with regard to the possibility of fluctuations for use in different periods. The daily use of opium was measured based on the local measurement unit "Nokhod" or its equivalent of 0.2 gr. The type of opioids used was divided into four types: raw opium (teriak), sap (shireh), burned opium (sukhteh), and heroin. In order to minimize the under-reporting of opium use in the control group, questions related to opium use and its derivatives were asked at the end of each interview. The interviewers were trained before-

hand and they gained enough experience to communicate effectively with people through a friendly environment. In this study heroine and burned opium use was not reported, therefore, only raw opium and sap entered the final analysis. Due to the relatively long time for cancer cells to develop, diet questions were asked for a minimum period of 10 years before the time of the interview. The diet part included the dietary habits of Iranians and especially the people of this area.

The study was approved by the Ethics Committee of Kerman University of Medical Sciences.

Data analysis

The amount of cigarette and opium cumulative use was calculated based on the amount of daily use and duration of use; and the participants were categorized into three groups: non-users, low users and high users. The median use in the control group was considered as a criterion for classifying the population into high and low use groups. People who used opioids and cigarettes in the study year were considered as current consumers. In addition, only a history of opioids use prior to diagnosis in cases was recorded in order to neutralize the effect of reverse causality.

Alcohol was classified into two categories of non-consumers and consumers, because of the low prevalence of its use in Iran. In addition, in this study the analyses were separately done in two groups of CRCs and colon cancer. Conditional logistic regression was used with 95% confidence intervals in order to estimate the adjusted odds ratios of opium use and its derivatives, cigarette, and alcohol with cancer risk. Moreover, only the variables with *P*-value less than 0. 1 in the univariate analysis were added to the final multivariate models. Multivariate logistic regression models were adjusted for total daily fruit and vegetables, red meat and hydrogenated fats. All statistical analyses were performed using STATA 12. 0 (Stata Corp, College Station, TX, USA).

Results

In this study, 175 cases and 350 controls were included. Among the cases, the majority (74. 2%) was male and 92. 0% were married. Most of the cases (51. 4%) were aged 51-70 yr and the least (15. 2%) were individuals aged less than 50 yr. More than half of the cases were illiterate or had primary school degree (52. 9%). In addition, 81. 2% of cases had colon cancer, 17. 8% had rectum cancer and 1. 0% had anal cancer. Other demographic information of cases and controls are summarized in Table 1. The average year of use in opioid drug users in both case and control groups was 27.7±11.8 and the most common age of onset of opioids use was between 20 to 30 yr and fumigant use was the most common method of use among cases (93. 0%) and controls (100%). In total, 25. 7% and 8. 0% of controls had a history of opioid use (*P*<0. 001). Results of univariate analysis showed that daily intake of fruit and vegetablesresult into reduced risk of CRCs; while consumption of red meat and hydrogenated fats might increase risk of the CRCs.

Table 2 shows the association between using opium, cigarette, and alcohol with CRCs. The use of opium and its derivatives are respectively associated with increased risk of all CRCs (OR: 4. 5; 95% CI: 2. 4- 8. 7) and colon cancers (OR: 5. 7; 95% CI: 2. 7- 11. 9). The amount of daily use of opium increased the risk of all CRSs and colon cancers, with adjusted ORs of 8. 0 (95% CI: 2. 8 – 22. 2), and 9. 2 (95 % CI: 3. 1 – 27. 4), respectively. In addition, the duration of opium use significantly increases the risk of all CRCs (OR: 8. 1; 95% CI: 2. 6-14. 6) and colon cancers (OR: 9. 0; 95% CI: 3. 0-27. 2). Moreover, in all CRCs, those who were still the current consumers were at greater risk for colorectal cancers than those who had a previous history of opium use. There was a dose-response relationship between opium use and the incidence of all CRCs (OR: 8. 0; 95% CI: 2. 9- 21. 7). The dose-response relationship was also observed in colon cancer (OR: 9. 4; 95% CI: 3. 3- 27. 0).

Table 1: Baseline characteristics of cases and controls

Variable	Matched controls	CRCs *	Matched controls	Colon cancer**
N	350	175	284	142
Gender		130 (74. 2)	220 (77. 4)	109 (76. 7)
Male	260 (74. 2)	45 (25. 8)	64 (22. 6)	33 (23. 3)
Female	90 (25. 8)			
P-value		0. 8		0. 8
Marital status				
Married	322 (92. 0)	168 (96. 0)	259 (91. 2)	137 (96. 4)
Single	28 (8. 0)	7 (4. 0)	25 (8. 8)	5 (3. 6)
P-value		0. 08		0. 07
Age				
≤ 50	56 (16. 0)	27 (15. 2)	48 (16. 9)	22 (15. 5)
51-70	167 (48. 0)	91 (51. 4)	136 (47. 9)	74 (52. 1)
> 70	125 (36. 0)	59 (33. 4)	100 (35. 1)	46 (32. 4)
P-value		0. 7		0. 7
Education				
Illiterate & elementary	185 (52. 9)	96 (54. 9)	147 (51. 8)	81 (57. 0)
Middle & high school	65 (18. 6)	23 (13. 1)	58 (20. 4)	17 (12. 0)
Diploma & above	100 (28. 5)	24 (32. 0)	79 (27. 8)	44 (31. 0)
P-value		0. 2		0. 1

*Includes colon, rectum, and anal cancers. ** Includes only colon cancer.

About 29. 1% of cases were smokers, while this rate was 24% for controls. Here, the multivariate analysis showed that being a smoker is not significantly associated with an increased risk of CRCs (OR 1. 5; 95 CI: 0. 9-1. 6) and colon cancer (OR: 1. 7; 95% CI: 0. 8-3. 1). The daily use of cigarettes had no statistically significant relationship with CRCs or colon cancer. In addition, the duration of using cigarettes had no statistically significant relationship with the risk of CRCs or colon cancer (Table 2).

No significant relationship was observed in multivariate analysis between cumulative use of cigarette smoking and CRCs (OR: 1. 6; 95% CI: 0. 7-3. 4). Similarly, the adjusted odds ratio was not significant in colon cancer either (OR: 2. 3; 95% CI: 1. 0 - 5. 2).

Alcohol use had a low prevalence and only about 3% of participants consumed alcohol, 3. 4% in the CRCs group and 2. 8% in the control group had a history of alcohol use. In this group, the adjusted odds ratio was not significant in multivariate analysis (OR: 1. 2; 95% CI: 0. 4-. 4. 9). Similarly, in the colon cancer group, alcohol use was not associated with an increased risk of colon cancer after adjustment for other confounding factors (OR: 1. 4; 95% CI: 0. 3-7. 0).

Discussion

This study aimed to investigate the relationship between opioid use and the risk of CRCs. The results of this study showed that opium use and its derivatives are associated with an increased risk of CRCs including colon, rectum and anal cancers. A dose-response relationship was observed between opium use and CRCs. The risk of incidence of these cancers increased withmore use of opioids.

Two types of opioidsin this study consisted of opium and sap and sap was less often used. For this reason, the odds ratio was calculated based on the concurrent use of sap and opium. Sap is usually made when opium is boiled (or by combining opium and pyrolysis residues after smoking opium) in water after multiple filtering (30). The reason of low sap prevalence in this study is not clear, but it may be due to at least two reasons including social undesirability of sap use and the commonbelief that sap use has more negative effects as compared with raw opium.

There are many possible reasons that intensify the existence of a causal relationship between opium and the incidence of CRCs. First, the strength of the relationship observed in this study is relatively significant and opium use increases the risk of CRCs and colon cancer about 4. 5 and 5. 7 times more. After controlling confounding factors such as diet (the use of fruits and vegetables, meat and oils), this relationship not only did not decrease, but also showed more strength.

In another study conducted in Kerman on the relationship between opium use and upper gastrointestinal cancers including esophageal cancer, opium use increased the risk of these cancers (20) and on the other hand other evidence have shown that patients with esophageal cancer have an increased risk of coexisting CRCs (40). This may indicate that the upper and lower gastrointestinal cancers have common risk factors which cause their simultaneous incidence. Although, no clear evidence has been reported on the relationship between opium and opioids with colorectal cancers and little evidence exists in this field; opium and opioids can increase the risk of cancers such as gastric (20, 24-25), larynx (22), bladder (21, 26-27), lung (23), esophagus (30, 41-42), oral cavity (28) and also the risk of death from these gastrointestinal cancers (43). This might confirm the carcinogenic effects of opioids.

Many mechanisms have been proposed regarding the relationship between opium use and the incidence of cancer. The use of opium and its alkaloids, including morphine may have mutagenic effects (42). In addition, empirical studies have shown that opium pyrolysis has mutagenic effects on Salmonella strains (44). In addition, pyrolysis and alkaloids of morphine lead to sister chromatic exchange in human lymphocytes and morphological changes in cultured Syrian hamster embryo cells (41). These drugs have caused

carcinogenic changes after being injected into tissues, under the skin, inside the trachea and into the gastrointestinal system of mice (42). In addition, many impurities are added to opioids during their processing in Iran and these chemicals may have carcinogenic effects. One of these chemicals is lead, which is added in order to make it heavier and for drug dealers to make more profit. In the studies conducted on addicted people, the amount of lead in the blood of these people is higher than the usual level and it is possible that the non-organic lead in these drugs causes severe toxic and even carcinogenic effects (36-37). In general, the carcinogenic mechanisms of opium have not been well identified and further studies are required to understand the carcinogenic mechanism of opium along with the relationship between opium and cancer.

While smoking is one of the main risk factors for these cancers (17-18, 45-46), in this study the association between smoking and the incidence of colorectal cancers was not statistically significant. Although, the reasons for this are uncertain but the low sample size and bias in reporting from families or the type and difference in cigarette from one region to another are the other reasons for the lack of this relationship and requires further studies. In fact, only 29. 1% of cases and 24. 9% of the controls had a history of smoking. This result was consistent with the results obtained in other studies in Iran (20, 24).

In this study, the confounding effect of diet on the relationship between opium and its derivatives with the incidence of CRCs was examined and the results showed that some foods, such as fruits and vegetables had a protective role and fats were risk factors. These results were consistent with the results of other studies carried out on the effect of diets with low calcium and fiber and with high fats and red meat in increasing the risk of colorectal cancers (11-16, 47-48).

Opioids use has a high prevalence in some parts of Iran such as the northern and southern areas. Based on the existing evidence, Kerman province is considered as one of the areas with high prevalence of opium use and its derivatives (32, 34). Moreover, studies suggest that these drugs can have a potential role in the increased incidence of these cancers in Iran.

This study also had some limitations. First, given the complexity of the relationship between cancer risk factors and according to methodological limitations, it cannot prove causality effect. One of the other limitations is the low sample size, which is due to the limited geographical area (only Kerman and its suburbs). Therefore, all the CRCs together were included in the study and colon cancer was later analyzed separately. In addition, all case-control studies are prone to recall bias, interviewer, and reporting bias during data collection. However, we attempted to control these by two trained and experienced interviewers. Another major limitation is that the alcoholuse is self-reported scale with social undesirability; therefore, it might consequently lead to an underreported estimate of actual alcohol for subjects. This issue makes a source of reporting bias for no significant association between alcohol use and CRCs. On the other hand, no association between cigarette smoking and CRCs was a result of limited numbers of pack used per year between both control and case groups that are consistent with the results of previous studies in Iran (20, 24, 30). The most important strength of this study was the pathological diagnosis of cancer, which minimized the probability of misclassification bias. The other strength of this study was using population-based neighbor controls rather than medical (hospital) controls which led to the control of the confounding socio-economic factors. Besides, this type of control selection led to better evaluation of the impact of the original exposure (29).

Conclusion

A remarkable part of the incidence of colorectal cancers at least in some parts of Iran is related to opium consumption. The results of this study are consistent with other reports of opium use and cancer, which may most likely indicate the causality of this relationship. However, more studiesare required.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgments

The authors declare that there is no conflict of interests.

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Table 2: The relationship between the use of opium and its derivatives, cigarette, and alcohol and the incidence of CRCs

Variable	CRCs				Colon 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	130 (74. 3)	322 (92. 0)	Reference	Reference	103 (72. 5)	258 (90. 9)	Reference	Reference
Ever	45 (25. 7)	28 (8. 0)	3. 8 (2. 2-6. 6)	4. 5 (2. 4-8. 7)	39(27. 5)	26(9. 1)	3. 7(2. 1-6. 6)	5. 7 (2. 7-11. 9)
Amount of daily opium use								
Never used	130 (74. 3)	322 (92. 0)	Reference	Reference	103 (72. 5)	258 (90. 9)	Reference	Reference
≤median **	21 (12. 0)	19 (5. 5)	2. 8 (1. 4-5. 4)	3. 9 (1. 7-9. 0)	18 (12. 6)	18 (6. 4)	2. 7 (1. 2-5. 7)	3. 4 (1. 3-8. 4)
>median	24 (13. 7)	9 (2. 5)	7. 1 (3. 0-16. 7)	8. 0 (2. 8-22. 2)	21 (14. 9)	8 (2. 7)	7. 3 (2. 9-18. 4)	9. 2 (3. 1-27. 4)
Duration								
Never used	130 (74. 9)	322 (92. 0)	Reference	Reference	103 (72. 5)	258 (90. 9)	Reference	Reference
≤median **	30 (17. 9)	21 (6. 0)	3. 2 (1. 2-5. 8)	3. 9 (1. 7-9. 1)	26 (18. 3)	19 (6. 7)	3. 4 (1. 7-6. 5)	4. 0 (1. 9-10. 1)
>median	15 (7. 2)	7 (2. 0)	3. 8 (2. 6-10. 6)	8. 1 (2. 6-14. 6)	13 (9. 2)	7 (2. 4)	4. 6 (1. 7-11. 8)	9. 0 (3. 0-27. 2)
Cumulative use of Opium***								
Never used	130 (74. 3)	322 (92. 0)	Reference	Reference	103 (73. 1)	252 (90. 0)	Reference	Reference
≤median**	21 (12. 0)	18 (5. 1)	2. 9 (1. 5-5. 7)	3. 7 (1. 6-8. 6)	16 (11. 4)	20 (7. 2)	3. 1 (1. 4-6. 0)	3. 9 (1. 5-9. 9)
>median	24 (13. 7)	10 (2. 9)	6. 5 (2. 8-14. 9)	8. 0 (2. 9-21. 7)	21 (15. 5)	8 (2. 8)	6. 6 (2. 7-16. 0)	9. 4 (3. 3-27. 0)
Cigarette smoking								
Never	124 (70. 9)	263 (75. 1)	Reference	Reference	95 (67. 9)	205 (73. 2)	Reference	Reference
Ever	51 (29. 1)	87 (24. 9)	1. 2 (0. 8-1. 9)	1. 5 (0. 9-1. 6)	45 (32. 1)	75 (26. 8)	1. 3 (0. 8-2. 0)	1. 7 (0. 8-3. 1)
Amount of daily tobacco use								
Never used	124 (70. 9)	263 (75. 1)	Reference	Reference	95 (67. 9)	205 (73. 2)	Reference	Reference
≤median **	28 (16. 0)	53 (15. 2)	1. 1 (0. 6-1. 6)	1. 4 (0. 6-2. 7)	25 (17. 8)	43 (15. 4)	1. 2 (0. 7-2. 2)	1. 6 (0. 5-3. 6)
>median	23 (13. 1)	34 (9. 7)	1. 5 (0. 6-2. 3)	1. 6 (0. 8-3. 4)	20 (14. 3)	32 (11. 4)	1. 3 (0. 7-2. 6)	1. 8 (0. 8-3. 7)
Duration								
Never used	124 (70. 9)	263 (75. 1)	Reference	Reference	95 (67. 9)	205 (73. 2)	Reference	Reference
≤median **	28 (16. 0)	54 (15. 5)	1. 1 (0. 5-1. 8)	1. 3 (0. 6-2. 7)	25 (17. 9)	48 (17. 2)	1. 1 (0. 6-1. 9)	1. 3 (0. 7-2. 3)
>median	23 (13. 1)	33 (9. 4)	1. 4 (0. 7-2. 7)	1. 7 (0. 8-3. 3)	20 (14. 1)	27 (9. 6)	1. 5 (0. 8-2. 9)	1. 7 (0. 5-3. 9)
Cumulative use of cigarette smoking***								
Never used	124 (70. 9)	263 (75. 1)	Reference	Reference	95 (67. 9)	205 (73. 2)	Reference	Reference
≤median**	25 (14. 3)	42 (12. 0)	1. 2 (0. 7-1. 9)	1. 4 (0. 8-2. 7)	23 (16. 4)	34 (12. 2)	1. 1 (0. 4-2. 1)	1. 4 (0. 6-2. 8)
>median	26 (14. 8)	45 (14. 9)	1. 3 (0. 6-2. 2)	1. 6 (0. 7-3. 4)	22 (15. 7)	41 (14. 6)	1. 4 (0. 6-2. 8)	2. 3 (1. 0-5. 2)
Alcohol use								
Never	169 (96. 6)	340 (97. 2)	Reference	Reference	136 (97. 1)	273 (97. 5)	Reference	Reference
Ever	6 (3. 4)	10 (2. 8)	1. 1 (0. 7-3. 3)	1. 2 (0. 4-4. 9)	4 (2. 9)	7 (2. 5)	1. 2 (0. 3-4. 2)	1. 4 (0. 3-7. 0)

*Confounding effect of specific dietary factors such as the use of meat, fruit and vegetables, hydrogenated fats, as well as other main exposures (cigarette) were controlled. **Median of use in the control group was considered as a criterion. ***Cumulative use was obtained by multiplying the amount of use (per day) and the duration of use (per year)