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ORIGINAL ARTICLE

Opium use and risk of colorectal cancer: a multi-center case-referent study in Iran

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ABSTRACT

Background: Opium use has been associated with an increased risk of cancers of the lung, oesophagus, and pancreas, and it was recently classified by the International Agency for Cancer Research as carcinogenic to humans. It is not clear whether opium also increases the risk of colorectal cancer (CRC). The aim of our study was to assess the association between various metrics of opium use and the risk of CRC.

Methods: This case-referent study from seven provinces in Iran comprised 848 CRC cases and 3215 referents. Data on opium use (duration, amount, frequency) and potential confounders were collected by trained interviewers. Multivariable unconditional logistic regression models were used to measure odds ratios (OR) adjusted for age, gender, province, marital status, family history of CRC-linked cancers, consumption of red meat, fruits and vegetables, body shape, occupational physical activity, and socio-economic status.

Results: Regular opium consumption was not associated with the risk of CRC (OR 0.9, 95% confidence interval, CI: 0.7, 1.2) compared to subjects who never used opium. However, frequent opium use more than twice a day was associated with an increased risk of CRC compared to non-users of opium (OR: 2.0, 95% CI: 1.1, 3.8; p for quadratic trend 0.008).

Conclusion: There seems to be no overall association between opium use and CRC, but the risk of CRC might be increased among persons who use opium many times a day.

Abbreviations: CRC: Colorectal cancer; SES: Socioeconomic status; OR: Odds ratios; CI: Confidence interval; FINJEM: Finnish job exposure matrix; PPWL: Physical activity workload

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Background

Colorectal cancer (CRC) is the third most common cancer and second most deadly malignancy, with 1.9 million incident cases and 0.9 million death worldwide in 2020 [1–3]. There were 1.2 million incident cases of colon cancers and 0.7 million rectal cancers worldwide in 2020, and the numbers are projected to increase until 2040 [1,2], mainly due to the increasing number of older persons [2]. Risk factors of CRC include age, obesity, lack of physical activity, red meat intake, and constipation [4]. Opium use causes constipation [5], and an excess risk of CRC among opium users is plausible through this mechanism. In Iran in 2014, CRC was the third most common cancer among men with an estimated age-standardized (World Standard) incidence rate (ASR) of 16.6/100 000 and the second most common cancer among women (ASR: 11.9/100 000) [6].

Opium, a highly addictive substance obtained from the unripe seedpod of the poppy plant, is illicitly consumed by millions of people worldwide, particularly in the Middle East and South Asia [7]. Freshly taken from the poppy plant, opium contains alkaloids (e.g., morphine, codeine, and thebaine). It is often minimally processed by heating, boiling, drying, and variably adulterated with some chemicals (e.g., lead or chromium) before it reaches consumers. In this minimally processed form, opium may be consumed as crude opium (teriak), opium juice (shireh), or opium dross (sukhteh) [8]. These forms of opium may be ingested or smoked.

Opium usually contains lead as an additive [9–12], and lead can cause constipation [13]. Since risk of CRC is elevated among those who suffer from constipation [13], we hypothesized that constipation might have an intermediate role between opium consumption and risk of CRC. Another mediator between opium use and risk of CRC may be poor oral hygiene. Opium use is associated with periodontal disease, and poor oral hygiene might increase risk of CRC [14].

An IARC Working Group in 2020 concluded that opium use has a carcinogenic effect on humans, based on sufficient evidence of carcinogenicity in humans for cancers of the lung, oesophagus, and pancreas [15]. The association between opium use and CRC is less clear. In two recent studies, opium use was suggested as a potential risk factor for CRC [16,17] while one study showed no association [18]. These studies suffered from limitations, such as small numbers of cases, reporting bias, lack of controlling for confounding variables, and lack of detailed information on opium use. In the present large-scale study, we report the association between various metrics of opium use and the risk of CRC.

Material and methods

The IROPICAN case-referent study was launched in ten provinces in Iran to assess associations between opium consumption and risk of cancers of the lung, CRC, bladder, and head and neck. These provinces were selected because the prevalence of opium use was relatively high and access to referral hospitals was possible. In this study we use data from only seven provinces since the data collection of CRCs was not performed in three centers in the southern part of Iran.

In the IROPICAN study, referents were enrolled concurrently with the cases among the relatives or friends of patients from non-oncology wards or others who visited the hospital for reasons other than receiving treatment. They were frequency-matched by gender, age, and province of residence, with cancer cases of all four cancer types combined. The referents had to be free of cancer at the date of recruitment. Trained interviewers conducted face to face interviews and collected data using a comprehensive validated questionnaire and 12 ml of venous whole blood for all cancer cases and referents. Details of the study have been described elsewhere [19].

For the current study, we used data of histologically confirmed incident primary CRCs (ICD-O-3: C18, colon; C19-20, rectum) and referents recruited from May 2017 until July 2020 [19]. The non-response rate among the cases was 1% and among the referents 11%. The main reasons for non-participation among the cancer patients were sickness and lethargy, and among the referents lack of time or unwillingness to donate a biological sample [19]. Forty cases with unknown subsite were excluded from the analysis. Altogether 848 CRC cases and 3215 referents were included in the study. The mean age at recruitment for the included cases was 58.7 (standard deviation 12.5) years and for the referents 57.2 (standard deviation 11.5) years.

Exposure assessment

Detailed histories of opium use were collected from cases and referents, including types of opium (crude opium, opium juice, and both types), routes of administration (only smoking, only ingestion, and both routes), duration of use, starting and stopping age, and daily amount and frequency of opium use. The amount of opium use was asked in local units of opium use which were converted to grams. All these metrics were answered for up to 5 separate periods of opium use, and the durations of these periods were used as weights in the calculation of weighted averages of the count per day (frequency), average amount of opium used at a time and daily dose of opium use.

In the statistical analyses, ever-use of opium was defined as using opium at least once during a lifetime, and regular opium use was defined as using opium at least once a week for at least six consecutive months. The cumulative amount of lifetime opium use was defined as the total duration of opium use (days) multiplied by the average daily amount, which was the product of an average amount of opium used at a time and the average daily frequency of opium use. We used a three-year lag time which means that possible opium consumption during the three last years before the interview date was excluded.

Potential confounders

Those who reported one or more of cancers of the colon, rectum, stomach, ovary and endometrium in their

Table 1. Numbers (and percentages) of subjects of colorectal cancer (CRC) cases and referents, by demographic characteristics and life habits.

Variable category	CRC cases	Colon cancer cases	Rectal cancer cases	Referents
Total	848 (100)	455 (100)	393 (100)	3215 (100)
Age at interview				
30-39	66 (7.8)	34 (7.5)	32 (8.1)	250 (7.8)
40-49	123 (14.5)	65 (14.3)	58 (14.8)	505 (15.7)
50-59	235 (27.7)	118 (25.9)	117 (29.8)	997 (31.0)
60-69	252 (29.7)	144 (31.7)	108 (27.5)	1020 (31.7)
≥70	172 (20.3)	94 (20.7)	78 (19.9)	443 (13.8)
Gender				
Female	366 (43.2)	198 (43.5)	168 (42.8)	1010 (31.4)
Male	482 (56.8)	257 (56.5)	225 (57.3)	2205 (68.6)
Place of residence				
Capital city of the region	538 (63.4)	300 (65.9)	238 (60.6)	1254 (39.0)
Other	310 (36.6)	155 (34.1)	155 (39.4)	1961 (61.0)
Province				
Tehran	170 (20.0)	100 (22.0)	70 (17.8)	816 (25.4)
Fars	248 (29.3)	102 (22.4)	146 (37.2)	943 (29.3)
Kerman	104 (12.3)	51 (11.2)	53 (13.5)	525 (16.3)
Golestan	140 (16.5)	92 (20.2)	48 (12.2)	374 (11.6)
Mazandaran	59 (7.0)	39 (8.6)	20 (5.1)	136 (4.2)
Kermanshah	66 (7.8)	32 (7.0)	34 (8.7)	251 (7.8)
Khorasan-Razavi	61 (7.2)	39 (8.6)	22 (5.6)	170 (5.3)
Socioeconomic status				
Low	325 (38.3)	173 (38.0)	152 (38.7)	863 (26.8)
Moderate	230 (27.1)	124 (27.3)	106 (27.0)	1085 (33.8)
High	293 (34.6)	158 (34.7)	135 (34.4)	1267 (39.4)
Body shape at age 15				
Normal	662 (78.1)	346 (76.0)	316 (80.4)	2694 (83.8)
Overweight	99 (11.7)	60 (13.2)	39 (9.9)	303 (9.4)
Obese	87 (10.3)	49 (10.8)	38 (9.7)	218 (6.8)
Physical activity at work				
Sedentary	282 (33.3)	157 (34.5)	125 (31.8)	1036 (32.2)
Medium	151 (17.8)	78 (17.1)	73 (18.6)	701 (21.8)
High	176 (20.8)	93 (20.4)	83 (21.1)	695 (21.6)
Unknown	239 (28.2)	127 (27.9)	112 (28.5)	783 (24.4)

first-degree relatives were defined as having a positive family history of cancer. These cancer types are possibly linked to Lynch syndrome or hereditary nonpolyposis colorectal cancer (HNPCC) [20,21].

We estimated perceived physical activity workload (PPWL) by using job histories of the participants and a Finnish job exposure matrix (FINJEM) [22,23]. In FINJEM there are two variables to estimate PPWL for each occupation, calendar period, the proportion of exposed (P), and mean level of the exposure among the exposed (L) [24]. We were not able to calculate the cumulative PPWL for the entire work life because of overlapping work periods in the collected data. Therefore, we only used PL for the longest work period, categorized into three categories: sedentary, moderate, or heavy (highest tertile of non-sedentary observations).

Numerous variables related to socioeconomic status (SES) were summarized using principal component analysis by combining data on years of education, and ownership of vacuum cleaner, dress washing machine, dishwashing machine, freezer, microwave, split air conditioner, laptop, internet access, mobile phone, personal car, owned house, or a shop. The weighted sums of these variables, where the weights are equal to the principal component loading, was categorized into tertiles and used in the logistic regression analyses as the SES variables.

Information about intake of 131 food items before the recruitment date was collected using a validated Persian cohort food frequency questionnaire [25]. For each food item, the reported daily frequency of consumption was multiplied by the standard portion size (grams). Consumption of red meat, fruit and vegetables was categorized into tertiles. Since we did not have information about height and weight in relevant ages to calculate body mass index, we classified body shape of the participants at age 15 into three categories (normal, overweight, obese) using data collected as pictograms which have been shown as a valid tool for such classification [26].

To define the constipation, participants were asked whether they have had constipation for more than six months. Number of decayed teeth was examined by trained interviewers and used as the index of oral hygiene, categorized based on the median (< 7, ≥7).

Statistical analyses

Unconditional logistic regression models were used to measure odds ratios (OR) and 95% confidence intervals (CI). The ORs were adjusted for age (ten-year age category), gender, and province, marital status, SES, body shape at age 15 years old, PPWL, family history of cancer, and intake of red meat and vegetables. Pack-year cigarette smoking, and energy intake were dropped from the final models because these variables did not significantly improve the model fit. In all analyses, non-users of opium were considered as the reference group.

To understand the existence and effect of the factors acting as possible mediators between opium and CRC, i.e.,

Table 2. Odds ratios (or) and 95% confidence intervals (CIs) for opium use, marital status, family history of cancer, red meat, vegetables, body shape, socioeconomic status, and perceived physical workload in risk of colorectal cancer, adjusted for age, gender, province, and all other cofactors listed in this table.

		Colorectal cancer		Colon cancer		Rectal cancer	
Variable category	Referents N (%)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Total	3215 (100)	848 (100)		455 (100)		393 (100)	
Opium use							
Non-user	2649 (82.4)	719 (84.8)	Ref.	386 (84.8)	Ref.	333 (84.7)	Ref.
Irregular	127 (3.9)	40 (4.7)	1.3 (0.9, 1.9)	25 (5.5)	1.4 (0.9, 2.3)	15 (3.8)	1.1 (0.6, 2.0)
Regular[a]	439 (13.7)	89 (10.5)	0.9 (0.7, 1.2)	44 (10)	0.8 (0.6, 1.2)	45 (11.5)	1.0 (0.7, 1.4)
Cofactors included in the model							
Marital status							
Married	2913 (90.6)	701 (82.7)	Ref.	374 (82.2)	Ref.	327 (83.2)	Ref.
Widow	164 (5.1)	99 (11.7)	1.9 (1.4, 2.6)	56 (12.3)	2.1 (1.4, 3.0)	43 (10.9)	1.8 (1.2, 2.6)
Divorced/separated	39 (1.2)	21 (2.5)	2.0 (1.1, 3.4)	10 (2.2)	1.8 (0.9, 3.9)	11 (2.8)	2.2 (1.0, 4.4)
Single	90 (2.8)	21 (2.5)	0.8 (0.5, 1.4)	12 (2.6)	1.0 (0.5, 1.8)	9 (2.3)	0.7 (0.4, 1.6)
Unknown	9 (0.3)	6 (0.7)	–	3 (0.7)	–	3 (0.8)	–
Socioeconomic status							
Low	863 (26.8)	325 (38.3)	Ref.	173 (38)	Ref.	152 (38.7)	Ref.
Moderate	1085 (33.8)	230 (27.1)	0.7 (0.5, 0.8)	124 (27.3)	0.7 (0.5, 0.9)	106 (27.0)	0.6 (0.5, 0.8)
High	1267 (39.4)	293 (34.6)	0.7 (0.6, 0.9)	158 (34.7)	0.8 (0.6, 1.0)	135 (34.4)	0.7 (0.5, 0.9)
Body shape at age 15							
Normal	2694 (83.8)	662 (78.1)	Ref.	346 (76)	Ref.	316 (80.4)	Ref.
Overweight	303 (9.4)	99 (11.7)	1.1 (0.9, 1.5)	60 (13.2)	1.3 (0.9, 1.8)	39 (9.9)	1.0 (0.7, 1.4)
Obese	218 (6.8)	87 (10.3)	1.3 (1.0, 1.8)	49 (10.8)	1.4 (1.0, 2.0)	38 (9.7)	1.3 (0.9, 1.9)
Perceived physical workload							
Sedentary	1036 (32.2)	282 (33.3)	Ref.	157 (34.5)	Ref.	125 (31.8)	Ref.
Medium	701 (21.8)	151 (17.8)	0.8 (0.6, 0.9)	78 (17.1)	0.7 (0.5, 1.0)	73 (18.6)	0.8 (0.6, 1.1)
High	695 (21.6)	176 (20.8)	0.8 (0.6, 1.0)	93 (20.4)	0.8 (0.6, 1.0)	83 (21.1)	0.8 (0.6, 1.1)
Unknown	695 (21.6)	239 (28.2)	0.6 (0.5, 0.8)	127 (27.9)	0.6 (0.4, 0.9)	112 (28.5)	0.6 (0.4, 0.9)
Family history of cancer							
No	3060 (95.2)	781 (92.1)	Ref.	419 (92.1)	Ref.	362 (92.1)	Ref.
Yes	155 (4.8)	67 (7.9)	1.7 (1.3, 2.3)	36 (7.9)	1.7 (1.2, 2.6)	31 (7.9)	1.7 (1.1, 2.6)
Red meat (g/day)							
< 12.83	1742 (54.2)	410 (48.4)	Ref.	215 (47.3)	Ref.	195 (49.6)	Ref.
12.83-25.64	990 (30.8)	233 (27.5)	1.3 (1.0, 1.5)	119 (26.2)	1.3 (1.0, 1.6)	114 (29.0)	1.3 (1.0, 1.7)
>25.64	480 (14.9)	205 (24.2)	2.2 (1.8, 2.7)	121 (26.6)	2.5 (1.9, 3.3)	84 (21.4)	1.9 (1.4, 2.6)
Unknown	3 (0.01)	–		–	–	–	–
Fruit and vegetables (g/day)							
<422	1606 (50.0)	409 (48.2)	Ref.	211 (46.4)	Ref.	198 (50.4)	Ref.
422-576	803 (25.0)	200 (23.6)	1.0 (0.8, 1.3)	108 (23.7)	1.2 (0.9, 1.5)	92 (23.4)	0.9 (0.7, 1.2)
>576	803 (25.0)	239 (28.2)	1.1 (0.9, 1.3)	136 (29.9)	1.3 (1.0, 1.7)	103 (26.2)	0.9 (0.7, 1.2)
Unknown	3 (0.01)	–		–	–	–	–

[a]Using opium at least once a week for at least six consecutive months during the lifetime. Some of them may have stopped opium use before the date of interview.

constipation and decayed teeth as an indicator of poor oral hygiene [27], we conducted a series of mediation analyses [28].

All statistical analyses were conducted using Stata, version 17 (Stata Corp, College Station, Texas 77845 USA, licensed to Tampere University).

Results

In the final study series, there were 455 cases of colon cancer and 393 cases of rectal cancer (Table 1). Out of 848 cases 89 (10.5%) and out of the 3215 referents 439 (13.7%) were regular opium users (Table 2).

Irregular opium use showed a non-significant 30% excess of CRC (Table 2). Regular opium use showed no association with risk of either CRC overall (OR: 0.9, 95% CI: 0.7, 1.2) or any of its two subsites (Table 2).

In analyses focusing to characteristics of opium use, ingestion of opium seemed to be associated with risk of rectal cancer (OR: 2.3, 95% CI: 1.0, 5.6) but not with colon cancer. The amount of opium used each time seemed not to affect risk of CRC (Table 3).

The frequency of opium use (count per day) was associated with an increasing risk of CRC (Table 3). Those who used opium more than two times per day had an OR of 2.0 (95% CI: 1.1, 3.8) compared to non-users of opium. Use of opium less than once per day showed an OR of 0.7 (95% CI: 0.5, 1.0). The quadratic p-trend related to the frequency of opium use for CRC was 0.008 (for colon 0.02, for rectum 0.1).

Among the cofactors included in the final model, red meat intake showed a strong association with the risk of CRC, more strongly for colon than rectum (Table 2). Obese persons showed a 30% higher risk of CRC than those with normal body shape. The risk of CRC was 70% higher among those who had first-degree relatives with HNPCC cancers than those without.

The mediation analysis showed that constipation and oral hygiene are mediators. However, the effect of opium use mediated *via* these factors was not strong, and hence the mediation analysis did not provide additional insight on the association between opium and risk of CRC. Therefore, we did not include constipation and oral hygiene in the final model.

Table 3. Odds ratios (or) and 95% confidence intervals (CIs) by characteristics of regular opium use from models adjusted for age, gender, province, marital status, family history of cancer, red meat, vegetables, body shape, socioeconomic status, and perceived p physical workload. Lag 3 years.

		Colorectal cancer		Colon cancer		Rectal cancer	
Metric of opium use category	Referents N (%)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95%CI)
Type of opium used							
No opium use	2649 (82.4)	719 (84.8)	Ref.	386 (84.8)	Ref.	333 (84.7)	Ref.
Crude opium (Teriak)	387 (12.0)	72 (8.5)	0.8 (0.6, 1.1)	34 (7.5)	0.8 (0.5, 1.2)	35 (8.9)	0.9 (0.6, 1.3)
Opium juice (Shireh)	31 (1.0)	9 (1.1)	1.3 (0.6, 2.8)	5 (1.1)	0.9 (0.3, 2.8)	7 (1.2)	1.6 (0.6, 4.4)
Both types	21 (0.7)	8 (0.9)	1.6 (0.7, 3.6)	5 (1.1)	1.6 (0.5, 4.9)	3 (0.8)	1.5 (0.5, 4.5)
Route of opium use							
Only smoking	368 (11.5)	69 (8.1)	0.9 (0.6, 1.2)	34 (7.5)	0.8 (0.6, 1.2)	35 (8.9)	0.9 (0.6, 1.3)
Only ingestion	27 (0.8)	12 (1.4)	1.6 (0.8, 3.2)	5 (1.1)	1.0 (0.4, 2.8)	7 (1.8)	2.3 (1.0, 5.6)
Both routes	41 (1.3)	8 (0.9)	0.9 (0.4, 2.0)	5 (1.1)	1.0 (0.4, 2.6)	3 (0.8)	0.8 (0.2, 2.7)
Unknown	3 (0.1)	–	–	–	–	–	–
Count per day[a]							
<1	308 (9.6)	48 (5.7)	0.7 (0.5, 1.0)	23 (5.1)	0.6 (0.4, 1.0)	25 (6.4)	0.8 (0.5, 1.2)
1-2	97 (3.0)	24 (2.8)	1.1 (0.7, 1.8)	12 (2.6)	1.1 (0.6, 2.1)	12 (3.0)	1.2 (0.6, 2.3)
>2	34 (1.1)	17 (2.0)	2.0 (1.1, 3.8)	9 (2)	2.0 (1.0, 4.5)	8 (2.0)	2.0 (0.9, 4.4)
Average opium uses at a time (g)							
<1	190 (5.9)	54 (6.4)	1.2 (0.9, 1.9)	28 (6.2)	1.1 (0.7, 1.8)	26 (6.6)	1.4 (0.9, 2.1)
1-2	140 (4.4)	18 (2.1)	0.6 (0.4, 1.0)	7 (1.5)	0.4 (0.2, 1.0)	11 (2.8)	0.7 (0.4, 1.4)
>2	109 (3.4)	17 (2.0)	0.7 (0.4, 1.2)	9 (2)	0.8 (0.4, 1.6)	8 (2.0)	0.7 (0.3, 1.4)
Daily dose of opium (g)[b]							
<1	233 (7.3)	46 (5.4)	0.9 (0.6, 1.2)	23 (5.1)	0.8 (0.8, 1.3)	23 (5.9)	1.0 (0.6, 1.6)
1-2	84 (2.6)	17 (2.0)	0.9 (0.5, 1.6)	9 (2)	0.9 (0.4, 1.9)	8 (2.0)	0.9 (0.4, 1.8)
>2	122 (3.8)	26 (3.1)	1.0 (0.6, 1.5)	12 (2.6)	0.9 (0.5, 1.8)	14 (3.6)	1.1 (0.6, 1.9)
Starting age of opium use							
<20	51 (1.6)	9 (1.1)	0.8 (0.4, 1.8)	5 (1.1)	0.9 (0.3, 2.3)	4 (1.0)	0.8 (0.3, 2.3)
20-29	134 (4.2)	20 (2.4)	0.7 (0.4, 1.2)	9 (2.0)	0.6 (0.3, 1.2)	11 (2.8)	0.9 (0.5, 1.7)
30-39	106 (3.3)	29 (3.4)	1.3 (0.8, 2.0)	16 (3.5)	1.3 (0.7, 2.3)	13 (3.3)	1.2 (0.7, 2.2)
≥40	148 (4.6)	31 (3.7)	0.8 (0.6, 1.3)	14 (3.1)	0.7 (0.4, 1.3)	17 (4.3)	1.0 (0.6, 1.7)
Time since stopping opium use							
Current user	213 (6.6)	41 (4.8)	0.9 (0.6, 1.3)	25 (5.5)	1.1 (0.9, 2.3)	16 (4.1)	0.8 (0.4, 1.3)
<10	133 (4.1)	31 (3.7)	1.0 (0.6, 1.5)	14 (3.1)	0.8 (0.5, 1.5)	17 (4.3)	1.2 (0.7, 2.0)
≥10	86 (2.7)	16 (1.9)	0.8 (0.5, 1.4)	5 (1.1)	0.5 (0.2, 1.3)	11 (2.8)	1.2 (0.6, 2.3)
Unknown	7 (0.2)	1 (0.1)	–	–	–	1 (0.3)	–
Duration of opium use (years)							
<19	254 (7.9)	60 (7.1)	1.0 (0.8, 1.4)	26 (5.7)	0.9 (0.6, 1.3)	34 (8.7)	1.2 (0.8, 1.8)
19-29	107 (3.3)	19 (2.2)	0.9 (0.5, 1.5)	13 (2.9)	1.2 (0.6, 2.2)	6 (1.5)	0.6 (0.3, 1.4)
>29	78 (2.4)	1 (1.2)	0.5 (0.3, 1.1)	5 (1.1)	0.5 (0.2, 1.2)	5 (1.3)	0.6 (0.2, 1.5)
Cumulative amount of opium (kg)[c]							
<4	211 (6.6)	45 (5.3)	0.9 (0.7, 1.3)	22 (2.2)	0.8 (0.5, 1.3)	23 (5.9)	1.1 (0.7, 1.7)
4 – 14	115 (3.6)	24 (2.8)	1.0 (0.6, 1.5)	10 (2.2)	0.8 (0.4, 1.5)	14 (3.6)	1.2 (0.6, 2.1)
>14	112 (3.5)	18 (2.1)	0.7 (0.4, 1.3)	11 (2.4)	1.0 (0.5, 1.7)	7 (1.8)	0.6 (0.3, 1.3)
Unknown	1 (0.0)	2 (0.2)	–	1(0.2)	–	1 (0.3)	–
Cumulative count of opium uses (times)[d]							
<4900	217 (6.8)	35 (4.1)	0.7 (0.5, 1.0)	17 (3.7)	0.7 (0.4, 1.1)	18 (4.6)	0.8 (0.5, 1.3)
4900-11000	126 (3.9)	30 (3.5)	1.1 (0.7, 1.8)	15 (3.3)	1.1 (0.6, 1.9)	15 (3.8)	1.2 (0.7, 2.2)
>11000	96 (3.0)	24 (2.8)	1.1 (0.7, 1.7)	12 (2.6)	1.0 (0.5, 1.8)	12 (3.1)	1.2 (0.6, 2.2)

[a]Duration-weighted average of the period-specific daily frequencies of opium use.
[b]Count per day multiplied by the average of opium use at a time (g).
[c]Cumulative amount: the average daily amount of opium multiplied by the total duration of opium use (days).
[d]Cumulative count: average count per day multiplied by the total duration of opium use (days).

Discussion

In this large multi-center case-referent study, regular opium use was generally not associated with risk of cancers of colon or rectum. Still, opium use of at least twice a day was associated with an approximately two-fold risk of CRC compared with the subjects who never used opium. The amount of opium used each time, or the duration and age span of opium use seemed not to affect the risk. Findings related to type and route of opium were also weak.

Few studies, two small case-referent studies and one cohort study, have evaluated the effect of opium use on the risk of CRC [16–18]. Our study showing lack of association with regular opium use is in line with the cohort study by Sheikh et al. [18]. In contrast, the two earlier case-referent studies showed a four-fold risk of CRC among opium users [16,17]. Both these studies used neighborhood referents. It has been reported that neighborhood controls may underestimate their opium use since using opium is not legal and users might not report it correctly [29]. In our study, instead, the referents were hospital visitors who were interviewed in identical way as the cases. It has been shown that in such a setting the completeness of reporting of opium use is similar among the cases and referents [30]. Still, there is chance of recall bias. The cases may report their opium use more likely than the referents. That would mean that our OR estimates are slightly too high.

To the best of our knowledge, our study is the first one that was able to evaluate the effect of frequency of opium use on the risk of CRC. In our data there was a trend of increasing CRC risk with increasing daily frequency of opium use, and use of opium more than twice a day carried a

two-fold risk of both cancers in colon and rectum. If these do not represent chance findings, we should seek for mechanisms how frequent opium use might increase risk of CRC. One possible mechanism considered *a priori* is constipation which can increase risk of CRC [13]. Lead as an additive of opium may lead to constipation [10]. A study by Nemati et al. showed that blood level of lead among opium users was three-fold as compared to non-users [31]. Although it is likely that frequent opium use increases risk of constipation, according to our data constipation appears not to have an important effect on the risk of CRC.

Heavy metals such as lead, arsenic, sulfate, chromium and cadmium as an opium additive [10,15] have been considered as risk factors for colon cancer; the plausible mechanism might be due to DNA damage along with dichromate ions to induce DNA methylation and gene silencing [32–34]. The study conducted by Sohrabi et al. showed that the mean concentration of lead in CRC tissues was approximately 2-fold as compared to that in healthy tissues [35]. The study by Etemadi et al. [36] showed that mortality and cancer risk might be increased due to presence of lead in the blood as a consequence of long term regular opium use. Our data did not include information on heavy metal intake of the cases and referents, and it was therefore not possible to assess direct effect of them on the CRC risk.

Because there is an association between frequency of opium use and risk of CRC, it would be expected that there also is an association between cumulative count of opium use and risk of CRC. We did however not observe any such association. The OR did not depend on the age of starting opium use nor on time since opium use had been stopped and increasing years of opium use rather decreased than increased the risk. It appears possible that opium users with constipation problems cannot continue opium use for a long time.

A study by Zu et al. [32] reported that opium use is associated with periodontal disease. Periodontal diseases might increase systemic inflammation, lead to immune system problems and alter gut microbiota, and probably influencing CRC carcinogenesis [14]. In our data number of decayed teeth used as an oral hygiene index did not show strong effect on the risk of CRC.

Another hypothetical mechanism that may explain the association of frequent opium use and increased risk of CRC could be related to polyps which are a confirmed risk factor of CRC [33,34]. If opium smoking increases risk of polyps in a similar way as has been shown for cigarette smoking [37] it would be possible that opium use may also indirectly increase the risk of CRC. We did not have data on polyps, but we suggest conducting studies on the effect of opium use on developing polyposis.

Our study had several strengths. The sample size was large, all CRC cases were histologically confirmed and correctly stratified as either colon or rectal cancer. We used healthy hospital visitor referents who do not share risk factors with the cases as might happen if the referents would be hospital patients with other diseases [30]. The data quality in our study was high because they were collected by trained interviewers using a validated questionnaire [19]. The response rate among both CRC patients and referents was high. Due to access to detailed information about details of opium use, we were able to examine the association of various metrics of opium use and risk of CRC. While accuracy of opium use information has been evaluated to be generally good, it has been shown that the assessment of amount of opium use is less reliable [38]. We do not know whether people who were asked to be referents differ in their opium consumption from the rest of the population. If they would be selected in terms of opium use, then we would have a selection bias. Therefore, we should be careful in interpreting the result in such a way that amount of opium use would have no effect.

In conclusion, although there seems to be no association between overall opium use and CRC, the risk of CRC might be increased among the persons who use opium more than twice a day.

Authors' contributions

MH did the literature review. HR, AN, MGH, MM, EM, RS, MS, BH, MB, RA, VA, SSH, AN, FN, AM, and AR contributed to data collection. FZ, RM, and MN provided clinical consultation. MH, HP, AR, RM, PB, EW, FK, KZ, and EP designed the study. MH and EP did the data analysis, interpreted data, and prepared the manuscript draft. All authors critically appraised the drafts of the manuscript and approved the final version. KZ is the guarantor of the study.

Authors' disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policies, or views of the International Agency for Research on Cancer/World Health Organization.

Ethical approval

The study was approved by the Ethics Committee of the National Institute of Medical Research Development (NIMAD) in Iran (Code: IR.NIMAD.REC.1394.027).

Consent to participate

Written informed consent was obtained from the parents.

Disclosure statement

There is no competing interest between authors.

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Data availability statement

The data underlying this article cannot be shared publicly due to privacy of individuals that participated in the study. The data may be shared on reasonable request to the corresponding author.

References

[1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249. doi: 10.3322/caac.21660.
[2] Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Transl Oncol. 2021;14(10):101174. doi: 10.1016/j.tranon.2021.101174.
[3] Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: an overview. Int J Cancer. 2021;149(4):778–789. doi: 10.1002/ijc.33588.
[4] Power AM, Talley NJ, Ford AC. Association between constipation and colorectal cancer: systematic review and meta-analysis of observational studies. Am J Gastroenterol. 2013;108(6):894–903; quiz 904. doi: 10.1038/ajg.2013.52.
[5] Fosnes GS, Lydersen S, Farup PG. Drugs and constipation in elderly in nursing homes: what is the relation? Gastroenterol Res Pract. 2012;2012:290231–290237. doi: 10.1155/2012/290231.
[6] Roshandel G, Ghanbari-Motlagh A, Partovipour E, et al. Cancer incidence in Iran in 2014: results of the iranian national population-based cancer registry. Cancer Epidemiol. 2019;61:50–58. doi: 10.1016/j.canep.2019.05.009.
[7] World Drug Report. United Nations publication, Sales No. E.20.XI.6 [Internet]. 2020. Available from: https://www.unodc.org
[8] Rahimi-Movaghar A, Gholami J, Amato L, et al. Pharmacological therapies for management of opium withdrawal. Cochrane Database Syst Rev. 2018;2018(6):CD007522. doi: 10.1002/14651858.CD007522.pub2.
[9] IARC. Opium consumption. IARC Monogr Identif Carcinog Hazards Hum. 2021;126:1–253.
[10] Hayatbakhsh MM, Oghabian Z, Conlon E, et al. Lead poisoning among opium users in Iran: an emerging health hazard. Subst Abuse Treat Prev Policy. 2017;12(1):43. doi: 10.1186/s13011-017-0127-0.
[11] Beattie AD, Briggs JD, Canavan JSF, et al. Acute lead poisoning: five cases resulting from self-injection of lead and opium. QJM Int J Med. 1975;44:275–284.
[12] Masoudi M, Zali MR, Ehsani M, et al. Abdominal pain due to lead-contaminated opium: a new source of inorganic lead poisoning in Iran. Arch Iran Med. 2006;9:72–75.
[13] Sundbøll J, Thygesen SK, Veres K, et al. Risk of cancer in patients with constipation. Clin Epidemiol. 2019;11:299–310. doi: 10.2147/CLEP.S205957.
[14] Momen-Heravi F, Babic A, Tworoger SS, et al. Periodontal disease, tooth loss and colorectal cancer risk: results from the nurses' health study. Int J Cancer. 2017;140(3):646–652. doi: 10.1002/ijc.30486.
[15] IARC Monographs Vol 126 Group. Carcinogenicity of Opium Consumption. Lancet Oncol. 2020;21:1407–1408.
[16] Naghibzadeh-Tahami A, Feyzabadi VY, Khanjani N, et al. Can opium use contribute to a higher risk of colorectal cancers? A matched case-control study in Iran. Iran J Public Health. 2016;45:1322–1331.
[17] Khosravizadegan Z, Naghibzadeh-Tahami A, Akbari M, et al. Opium use and risk of lower gastrointestinal cancers: population-Based Case-Control study in South of Iran. Int J Cancer Manag. 2017;10(6):e8227. doi: 10.5812/ijcm.8227.
[18] Sheikh M, Shakeri R, Poustchi H, et al. Opium use and subsequent incidence of cancer: results from the golestan cohort study. Lancet Glob Health. 2020;8(5):e649–60–e660. doi: 10.1016/S2214-109X(20)30059-0.
[19] Hadji M, Rashidian H, Marzban M, et al. The iranian study of opium and cancer (IROPICAN): rationale, design, and initial findings. Arch Iran Med. 2021;24(3):167–176. doi: 10.34172/aim.2021.27.
[20] Hampel H, Frankel WL, Martin E, et al. Screening for the lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med. 2005;352(18):1851–1860. doi: 10.1056/NEJMoa043146.
[21] Peltomäki P, Olkinuora A, Nieminen TT. Updates in the field of hereditary nonpolyposis colorectal cancer. Expert Rev Gastroenterol Hepatol. 2020;14(8):707–720. doi: 10.1080/17474124.2020.1782187.
[22] Kauppinen T, Toikkanen J, Pukkala E. From cross-tabulations to multipurpose exposure information systems: a new job-exposure matrix. Am J Ind Med. 1998;33(4):409–417. doi: 10.1002/(SICI)1097-0274(199804)33:4<409::AID-AJIM12>3.0.CO;2-2.
[23] Kauppinen T, Uuksulainen S, Saalo A, et al. Use of the finnish information system on occupational exposure (FINJEM) in epidemiologic, surveillance, and other applications. Ann Occup Hyg. 2014;58:380–396.
[24] Pukkala E, Guo J, Kyyrönen P, et al. National job-exposure matrix in analyses of census-based estimates of occupational cancer risk. Scand J Work Environ Health. 2005;31(2):97–107. doi: 10.5271/sjweh.856.
[25] Poustchi H, Eghtesad S, Kamangar F, et al. Prospective epidemiological research studies in Iran (the PERSIAN cohort study): rationale, objectives, and design. Am J Epidemiol. 2018;187(4):647–655. doi: 10.1093/aje/kwx314.
[26] Keshtkar AA, Semnani S, Pourshams A, et al. Pictogram use was validated for estimating individual's body mass index. J Clin Epidemiol. 2010;63(6):655–659. doi: 10.1016/j.jclinepi.2009.08.014.
[27] Etminan M, Collins GS, Mansournia MA. Using causal diagrams to improve the design and interpretation of medical research. Chest. 2020;158(1S):S21–S28. doi: 10.1016/j.chest.2020.03.011.
[28] VanderWeele T. Explanation in causal inference: methods for mediation and interaction. New York, NY: Oxford University Press; 2015.
[29] Mohebbi E, Rashidian H, Tahami AN, et al. Opium use reporting error in case-control studies: neighborhood controls versus hospital visitor controls. Med J Islam Repub Iran. 2021;35:60–67.
[30] Rashidian H, Hadji M, Marzban M, et al. Sensitivity of self-reported opioid use in case-control studies: healthy individuals versus hospitalized patients. PLoS One. 2017;12(8):e0183017. doi: 10.1371/journal.pone.0183017.
[31] Nemati A, Jafari S, Afshari M, et al. Comparing blood lead level among oral/inhaled opium addicts with a non-addict control group in the southeast of Iran. Addict Health. 2016;8:235–241.
[32] Wu Z, Han Y, Caporaso JG, et al. Cigarette smoking and opium use in relation to the oral microbiota in Iran. Microbiol Spectr. 2021;9(2):e00138-21. doi: 10.1128/Spectrum.00138-21.
[33] Karstensen JG, Burisch J, Pommergaard H-C, et al. Colorectal cancer in individuals with familial adenomatous polyposis, based on analysis of the danish polyposis registry. Clin Gastroenterol Hepatol. 2019;17(11):2294–2300.e1. doi: 10.1016/j.cgh.2019.02.008.
[34] Bodmer WF, Bailey CJ, Bodmer J, et al. Localization of the gene for familial adenomatous polyposis on chromosome 5. Nature. 1987;328(6131):614–616. doi: 10.1038/328614a0.
[35] Sohrabi M, Gholami A, Azar MH, et al. Trace element and heavy metal levels in colorectal cancer: comparison between cancerous

and non-cancerous tissues. Biol Trace Elem Res. 2018;183(1):1–8. doi: 10.1007/s12011-017-1099-7.

[36] Etemadi A, Hariri S, Hassanian-Moghaddam H, et al. Lead poisoning among asymptomatic individuals with a long-term history of opiate use in golestan cohort study. Int J Drug Policy. 2022;104: 103695. doi: 10.1016/j.drugpo.2022.103695.

[37] Botteri E, Iodice S, Raimondi S, et al. Cigarette smoking and adenomatous polyps: a meta-analysis. Gastroenterology. 2008;134(2): 388–395. doi: 10.1053/j.gastro.2007.11.007.

[38] Mohebbi E, Kamangar F, Rahimi-Movaghar A, et al. An exploratory study of units of reporting opium use in Iran: implications for epidemiologic studies. Arch Iran Med. 2019;22: 541–545.