Gastroenterology and Hepatology From Bed to Bench.
2024 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

SYSTEMATIC REVIEW

p-ISSN: 2008-2258 e-ISSN: 2008-4234

Opium use and gastrointestinal cancers: a systematic review and meta-analysis study

Mahsa Mohammadi[1], Philippe Tadger[2], Amir Sadeghi[3], Niloufar Salehi[3], Mohsen Rajabnia[4], Elham Paraandavaji[3,9], Sasan Shafiei[3,9], Ahmad Pirani[5], Mohammad Reza Hatamnejad[3], Erfan Taherifard[6], Fatemeh Kheshti[6], Arman Naderilordejani[3], Forough honarfar[3], Khaled Rahmani[3], Majid Soruri[3], Hamed Kord Varkaneh[3], Omid Dadras[7,8], Ali Jahanian[3], Sara Rasta[4], Mohammad Reza Zali[3]

[1]*Gastrointestinal and Liver Diseases Research Center, Guilan University of Medical Sciences, Guilan, Iran*
[2]*Real World Evidence, IQVIA, 3600 Genk, Belgium*
[3]*Gastroenterology and Liver Disease Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[4]*Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran*
[5]*Mental Health Research Center, Iran University of Medical Sciences, Tehran, Iran*
[6]*School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*
[7]*Department of Global Public Health and Primary Care, University of Bergen, Norway*
[8]*Section Global Health and Rehabilitation, Western Norway University of Applied Science, Norway*
[9]*Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

ABSTRACT

Aim: The current systematic review and meta-analysis aimed to assess the association between Gastrointestinal (GI) cancers and opium use.

Background: GI malignancies are a global public health issue and are associated with many risk factors including genetic and lifestyle factors.

Methods: PubMed, Web of Science, Embase and Scopus and the Google Scholar search engine in addition to Persian databases including Magiran and SID were searched using relevant keywords. The associations of opium use, long duration of opium use, high daily amount opium use and high cumulative opium use and GI cancer and various subtypes of GI cancers were estimated and pooled in format of odds ratios (OR) and their corresponding 95% confidence intervals (CI) with a random effects model.

Results: 22 articles that were published between 1983 and 2022 entered the analyses. There were significant relationships between opium use based on crude effect sizes (OR: 2.53, 1.95-3.29) and adjusted effect sizes (OR: 2.64, 1.99-3.51), high daily opium use (or: 3.41, 1.92-6.06), long duration of opium use (OR: 3.03, 1.90-4.84) and high cumulative opium use (OR: 3.88, 2.35-6.41), all compared to never opium use, and GI cancer. The results were not sensitive to sensitivity analyses and no influential publication biases were found in these analyses.

Conclusion: Our meta-analysis showed that opium use could be associated with increased risk of overall and some particular GI cancers including oropharyngeal, gastric, pancreatic and colorectal cancers. Opium use as a potentially modifiable factor, therefore, should be more emphasized.

Keywords: Opium, Gastrointestinal tract, Cancer, Meta-analysis.

(Please cite as: **Mohammadi M, Tadger P, Sadeghi A, Salehi N, Rajabnia M, Paraandavaji E, Shafiei S, Pirani A, Hatamnejad MR, Taherifard E, Kheshti F, Naderilordejani A, Honarfar F, Rahmani K, Soruri M, Kord Varkaneh H, Dadras O, Jahanian A, Rasta S, Zali MR. Opium use and gastrointestinal cancers: a systematic review and meta-analysis study. Gastroenterol Hepatol Bed Bench 2024;17(2):104-120. https://doi.org/10.22037/ghfbb.v17i2.2882).**

Introduction

Cancer is a global public health issue with a major burden of disease. According to data provided by the World Health Organization, cancer is the main cause of death in the world after ischemic heart disease (1).

Received: 23 October 2023 *Accepted*: 02 February 2024
Reprint or Correspondence: **Mohsen Rajabnia,** *Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Golshahr, 31987-64653 Karaj, Iran.*
E-mail: dr.rajabnia@outlook.com
ORCID ID: 0000-0002-3123-4315

Furthermore, new cases and deaths caused by cancer in 2020 were estimated to be 19.3 and 10.0 million, respectively. In addition, this global public health issue is reported to be attributed to the highest proportion of Disability-Adjusted Life Years compared to all other diseases (2). Four out of the ten most common cancers are gastrointestinal (GI) malignancies including colorectal (10%), gastric (5.6%), liver (4.7%), and esophageal (3.1%) cancers (3). Despite the advances in medical sciences and practice, the mortality rate and burden of GI cancer are still increasing due to its risk factors (4), especially in middle- and low-income countries (5). The proposed risk factors of GI cancer could be divided into genetic factors such as race and family history and lifestyle factors such as opium use, cigarette smoking, alcohol consumption, obesity, low fiber consumption, and increased fat intake (6-8).

The first study that assessed opium use as a risk factor of GI cancer was conducted in the 1970s (9). Since then, several articles have focused on this issue, most of which have been undertaken in Iran. This substance is highly addictive and commonly been used by people in countries in the Middle East. Opium is commonly used in four ways: raw (teriak), sap (shireh), burned dross left in the pipe (sukhteh), and heroin (10). In Iran, opium consumption has a traditional supporting culture as opioids have been used for their pain relief, analgesic, and hypnotic effects. In addition, it has been traditionally believed that consuming small amounts of opium could prevent chronic diseases especially those related to cardiovascular system (11).

To best of our knowledge, there are two published meta-analysis study assessing the relationship between opium use and development of all types of cancer (12, 13). In the systematic review and meta-analysis conducted by Mansouri et al., the results of several studies published before the date of its search have not been included (14-16). In the other review study, a wide and comprehensive assessment of different route of opium use, the duration of use, daily amount use of opium, etc. was not performed. Besides, there are also several studies that were published after these meta-analyses (17-19). Therefore, we aimed to conduct an updated meta-analysis, we aimed to combine the results of all the primary studies to estimate the association between different aspects of opium use and various GI cancers.

Methods

Search strategy and study selection

The aim of the current systematic review and meta-analysis was to evaluate the association between opium use and various GI cancers including oral, esophageal, gastric, pancreatic, hepatobiliary, colorectal cancers. The review study was conducted using Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline (20). Online databases including PubMed, Web of Science, Scopus, and Embase were searched systematically using relevant MeSH headings and keywords; we used three world group for our systematic search. For keywords related to opium consumption, “opium”, “papaveretum”, “omnopon”, “pantopon”, “papaver”, “poppy”, “teriak”, “shireh” , “sukhteh”, “afioon” and “khashkhaash”, for keywords related to cancer, “cancer”, “neoplasm”, “neoplasia”, “tumor”, “carcinoma”, “malignancy” and “malignancies” and for keywords related to gastrointestinal system, “GI”, “gastrointestinal”, “alimentary”, “mouth”, “oral”, “esophagus”, “esophageal”, “gastric”, “cardia”, “stomach”, “intestine”, “intestinal”, “bowel”, “duodenum”, “duodenal”, “jejunum”, “jejunal”, “ileum”, “ileal”, “colon”, “rectum”, “rectal”, “anus”, “anal”, “colorectal”, “pancreas”, “pancreatic”, “liver”, “hepatic”, “hepatocellular”, “cholangiocarcinoma” and “gallbladder”. First 200 results following the search in Google Scholar were also assessed. The systematic search was also conducted in Persian databases of Magiran (magiran.com) and SID (sid.ir). Using Magiran search engine, we also searched the keywords in grey literature such as Persian newspapers. The primary search was done in July 1, 2022 and then, was updated in January 3, 2023. The search strategy used in PubMed database is provided in Supplementary material.

The records found in the search were imported into Endnote Library. Two independent individuals screened and selected the studies first based on their titles and abstracts and afterwards, by assessing the full-texts of the studies. Intraclass Correlation Coefficient (ICC) was used to assess the agreement between the independent individuals involved in the studies' selection process. If each screener provides numerical scores (e.g., on a scale of 1 to 10), ICC can be used to evaluate how closely their scores align. Regarding reviewer discrepancies, a third researcher,

the corresponding author, conducted the final evaluation and decided on inclusion/exclusion meriting.

Inclusion criteria

The inclusion criteria included: 1) English and Persian articles published until January 3, 2023, 2) Studies with observational designs of cohort, cross-sectional, and case-control, 3) Publications that included cases diagnosed with any type of GI cancer, 4) Publications that the participants were compared with a control/cohort group in terms of opium consumption, and 5) Studies that evaluated opium use by only questioning the participants. Therefore, studies that included opium users with a positive urine test or other methods were excluded.

Data extraction

The full-texts of the relevant publications were assessed; all data were extracted independently by two researchers and summarized in a Microsoft Excel spreadsheet. Name of first author, year of publication and years of patients' referral, design of each study, location of participant enrollment, characteristics of the study participants, number of cases and controls/cohorts, the prevalence of opium consumption in each group, crude and adjusted odds/hazard ratios (ORs/HRs), and their 95% confidence intervals (CIs) were collected.

Quality assessment

In the current study, we used Newcastle-Ottawa Scale to assess the quality of the included studies (21). The process of quality assessment was conducted by two authors independently and then, in the case of any disagreement, they discussed that with a third author. With this scale, articles are assessed for quality based on their selection process, comparability, assessment of the exposure/outcomes. Articles with scores of less than 5 are considered to have low-quality.

Statistical analysis

We used Comprehensive Meta-Analysis (Biostat Inc., CO, USA) version 3 for data management and analysis. The associations of opium use, opium ingestion, opium smoking, teriak consumption and shireh consumption and GI cancer and various subtypes of GI cancers were estimated. We also conducted separate quantitative analyses on the studies reporting the relationship between "high" daily use of opium, "long" duration of opium use, and "high" cumulative use of opium, all were defined by the corresponding median of the control group. These variables were assessed in the studies on the basis of the total unit of opium each day on average, the total years one consumed opium and the unit-year use of opium, respectively. These associations were pooled in format of ORs and their corresponding 95% CIs with a random effects model. In the articles that ORs were not reported, we calculated the crude OR using the numbers of patients with and without cancers and the proportion of opium use among each group. We also pooled the crude adjusted ORs and CIs and adjusted ORs and CIs, separately. We assessed inter-study heterogeneity using Cochran's Q test and I2 statistic. Sensitivity analyses and subgroup analyses were also conducted. The subgroup analyses were performed based on current or ever use of opium, different subtypes of GI cancers and different designs of studies (case-control studies and cohort studies). Egger's test was used to detect potential publication bias for analyses with at least 10 studies. For those quantitative analyses that the Egger's test was indicative of presence of a potential publication bias, Duval and Tweedie's trim and fill analysis was conducted to assess whether the addition of missing studies would change the significancy of the results. P-values less than 0.05 were considered as statistically significant.

Results

Search results

Following our systematic search in online databases, 168 records in PubMed, 295 records in Scopus, 215 records in Embase and 212 records in Web of Science were found and then were evaluated in the endnote Library. Among these records, 378 records were found automatically by the Endnote's duplicate finder and removed from the library. The remaining records were evaluated based on their title and abstract and in this step, 484 records were removed. 8 additional records with relevant title/abstract were yielded in other databases including Magiran, SID and Google Scholar. In the next step, full-texts of these records, 36 records, were retrieved and assessed. Among them, 14 studies were found to be ineligible and a total of 22 articles entered the quantitative analysis. Of 14 ineligible studies, in 8 studies, there was insufficient data, in 3 studies, there was no control group, in 2 studies and in one study, the population was same as another (Figure 1).

Characteristics of the included studies

Characteristics of the twenty-two eligible articles included in our study are presented in Table 1. These articles assessed the association of opium consumption and various GI cancers. The articles were published between 1983 and 2022 and all of them were carried out in Iran. Of them, the majority, 19 studies (86.4%) were case-control studies, 2 were cohort and 1 was in both designs of case-control and cohort. Only in two studies the association of opium use with all types of GI cancers were assessed. In other studies, the association of opium use and a particular GI cancer was investigated. These studies contain details of 68546 individuals with 5897 of them having various types of GI cancers. In overall, there were 1357 patients with colorectal cancer, 1275 patients with esophageal cancer, 1181 patients with gastric cancer, 1104 patients with pancreatic cancer, 803 patients with oropharyngeal cancer and 209 patients with liver cancer.

Meta-analysis results

The numbers of opium use among individuals with and without various types of GI cancer and the individualized associations of opium use, long duration of opium use, high daily amount opium use and high cumulative opium use, opium ingestion, opium smoking, teriak consumption and shireh consumption and GI cancer in format of crude and adjusted ORs are provided in Supplementary Table 1. Despite disparities in measuring the duration and dosage of opium use, long periods and high cumulative doses of opium were considered for the values higher than median. Besides, the result of quality assessment of the included articles is included in this table; no article had low quality and they, all, had acceptable quality.

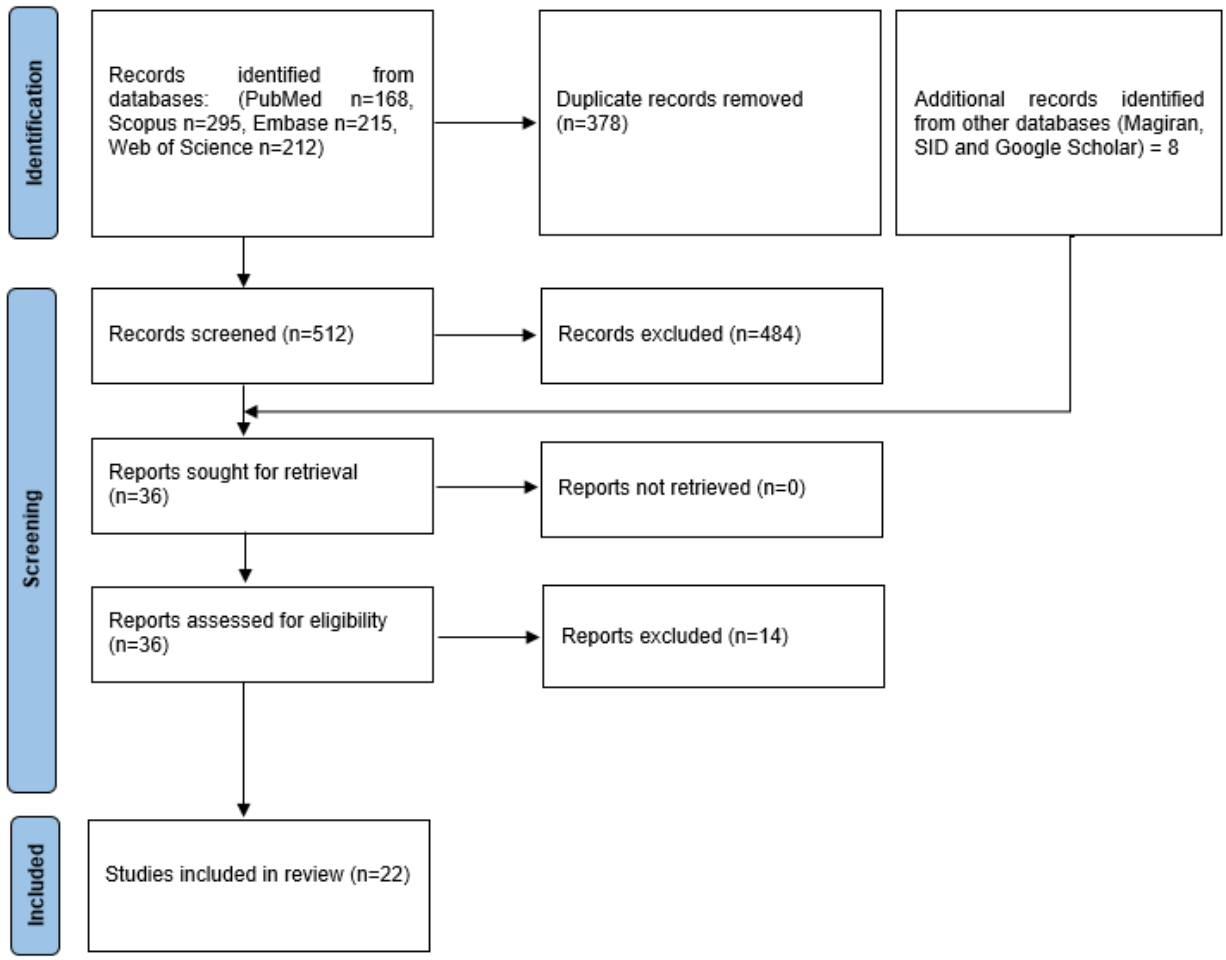


Figure 1. PRISMA 2020 flowchart of study identification, screening and selection process

Table 1. Characteristics of the studies included in this systematic review and meta-analysis on the association of opium use and GI cancer

First author, date of publication	Design of study	Country (city/province)	Study year	Type of cancer	Numbers of patients with and without cancer	Mean age (SD)	Male/ Female (%)	Characteristics of the participants without cancer	Opium use	Variables considered in adjustment
Marzban et al. 2022 (22)	Case-control	Iran (Kerman)	2016-2018	Primary liver cancer	117/234	63.2 (13.3)	2.1	Age and sex matched healthy neighbors without history of any cancers	Opium ever use	Cigarette smoking, marital status and education
Collatuzzo et al. 2022 (17)	Case-control	Iran (multicenter)	2017-2020	Colorectal cancer, colon (50%), rectum (47%), other	865/3205	57.4 (11.7)	1.8	Age, sex and place of residence matched hospital visitors without history of cancer	Opium ever use	-
Momayez Sanat et al. 2021 (19)	Case-control	Iran (Tehran)	2012-2018	Pancreatic ductal adenocarcinoma	470/526	63.4 (12.4)	1.5	Age and sex matched patients with normal pancreas in the EUS exam with no history of cancer and no pancreatic disease or any cancers 1 year after the initial visit	Ever use at least weekly for a period of 6 months not initiated within the year prior to the diagnosis	Age, sex, smoking status, BMI, and family history of cancer in the first-degree relatives
Naghibzadeh Tahami et al. 2021 (23)	Case-control	Iran (Kerman)	2016-2018	Pancreatic cancer	176/352	NM	1.6	Age and sex matched healthy neighbors without history of any cancers	Ever opium users were defined as using for least on a weekly basis for 6 months	BMI, tobacco use, cigarette smoking, and alcohol use, diet and education
Mohebbi et al. 2020 (24)	Case-control	Iran (multicenter)	2016-2019	Squamous cell carcinoma of oral cavity and pharynx	308/3065	NM	NM	Age, sex and place of residence matched hospital visitors without history of cancer	Regular opium using opium at least once a week for at least months not initiated within 3 years before the diagnosis	Age, gender, place of residence, cigarette smoking, water-pipe smoking, alcohol drinking, decayed, missing and filled teeth index and socioeconomic status
Sheikh et al. 2020 (25)	Cohort	Iran (Golestan)	2004-2008	All types of cancer	914/49120	52.0 (8.9)	0.7	NA	Regular opium users as those who used opium at least once a week for at least 6 months	Sex, ethnicity, residence, wealth score, smoking cigarettes, cumulative pack-years of smoked cigarettes, regular alcohol drinking, chewing Nass, regular consumption of hookah, predominant household fuel and diet
Vazirnejad et al. 2020 (26)	Case-control	Iran (Rafsanjan)	2018	GI cancers, esophagus (43%), colorectal (41%), stomach (8%), pancreas (7%), other	95/190	58.2 (15.5)	1.3	Healthy individuals from relatives and neighbors matched for age, sex, place of residence and smoking	Current opium use who initiated opium use more than one year before the diagnosis	Education level, family history of cancer and diet
Pournaghi et al. 2019 (15)	Case-control	Iran (North Khorasan)	2013–2015	Squamous cell carcinoma of esophagus	96/187	NM	0.8	Age and sex matched hospitalized individuals	Current or previous use of opium	-

Continues

Lankarani et al. 2017 (27)	Case-control	Iran (Shiraz)	2014-2015	Colorectal cancer, colon (58%), rectum (30%), anus (12%)	160/320	NM	1.3	Age and sex matched individuals from cases' neighbors	Opium ever use	All variables with p-value less than 0.1 were inserted in the model, smoking and diet
Bakhshaee et al. 2017 (28)	Case-control	Iran (Mashhad)	2008- 2010	Squamous cell carcinoma of esophagus	95/28	NM	NM	Age matched healthy individuals with no evidence of head and neck or esophageal malignancies	Using for at least once a day for a minimum of one year	Age, sex and smoking
Shakeri et al. 2016 (29)	Case-control	Iran (Tehran)	2011-2015	Pancreatic ductal adenocarcinoma	357/328	64.6 (11.6)	1.1	Age and sex matched patients with normal pancreas in the EUS exam with no history of cancer and no pancreatic disease or any cancers 1 year after the initial visit	Ever use at least weekly for a period of 6 months not initiated within the year prior to the diagnosis	Age, sex, place of residence, alcohol use and ever use of any type of tobacco
Naghibzadeh Tahami et al. 2016 (30)	Case-control	Iran (Kerman)	2012- 2014	Colorectal cancer, colon (81%), rectum (18%), anus (1%)	175/350	NM	1.4	Age and sex matched individuals from cases' neighbors	Opium ever use	Marital status and diet
Razmpa et al. 2014 (31)	Case-control	Iran (Tehran)	2008- 2010	Squamous cell carcinoma of oral cavity, tongue (57%), lip (19%), buccal mucosa (11%), other	80/80	58.3 (13.9)	1.7	Age and sex matched healthy individuals with same socioeconomic status mainly from cases' family	Opium dependency for at least 5 years	Alcohol consumption and smoking
Hakami et al. 2014 (32)	Case-control	Iran (Gonbad)	NM	Squamous cell carcinoma of esophagus	40/80	62.5 (11.3)	0.9	Age and sex matched individuals with no upper GI cancer on endoscopy and no family history	Opium ever use	-
Naghibzadeh Tahami et al. 2014 (33)	Case-control	Iran (Kerman)	2010- 2012	Upper GI cancers, gastric (63%), liver (13%), pancreas (11%), esophagus (10%), oral cavity (2%)	142/284	NM	2.7	Age and sex matched individuals from cases' neighbors	Opium ever use before the diagnosis	Smoking, alcohol use, diet and educational level
Sadjadi et al. 2014 (34)	Cohort	Iran (Ardabil and Meshkinshahr)	NM	Gastric cancer	36/892	NM	NM	NA	Use of opium for at least once a week for the last 6 months	Age, gender, family history of cancer, cigarette smoking, hookah smoking, alcohol use and diet
Shakeri et al. 2013 (35)	Case-control	Iran (Gonbad)	2004- 2011	Gastric adenocarcinomas, cardia (52%) and non-cardia (38%) adenocarcinomas, mixed or unknown site (10%)	309/613	64.0 (9.5)	2.7	Age, sex and neighborhood-matched controls	Ever user of opium as use of product at least once a week for a minimum of 6 months	Ethnicity, education, wealth score, diet, hookah, Nass and cigarettes

Continues										
Shokri-Shirvani et al. 2013 (36)	Cross-sectional	Iran (Babol)	2005-2009	Gastric cancer, Fundus (30%), antrum (25%), body (22%), other	281/680	57.5 (17.2)	1.7	Individuals for whom gastric ulcer was detected upon endoscopy	Opium use for more than 1 year and ≥3 times a week either smoking or ingestion	-
Shakeri et al. 2012 (37) and Nasrollahzadeh et al. 2008 (38)	Case-control	Iran (Gonbad)	Pilot phase (2002–2003)	Esophageal squamous cell carcinoma	130/260	-	1.5	Age and sex matched hospitalized individuals	Opium ever use	Age, sex, and place of residence, education, ethnicity and use of cigarette, hookah and Nass
			Main phase (2004–2007)		300/571	64.4 (10.3)	1	Age and sex, place of residence matched individuals from neighbors		Education, ethnicity, diet and tobacco use
Islami et al. 2004 (16)	Case-control	Iran (Golestan)	2001-2003	Squamous cell carcinoma of esophagus (60%), adenocarcinoma of esophagus (6%), gastric cardia and non-cardia adenocarcinoma (both 16%), other	370/284	NM	1.3	Individuals with no endoscopically suspicious lesion	Opium use more than 1 year before the diagnosis	-
Fahmy et al. 1983 (39)	Case-control and cohort	Iran (Shiraz)	1962- 1978	Oral cancer, lip cancer (50%), tongue (20%), other	381/1000	55 (26.6)	1.5	Individuals matched for age group and socioeconomic status	Having opium addiction	-

To assess, the association of opium use and GI cancer, we pooled 24 crude ORs and 16 adjusted ORs, separately, using random effects model (Figure 2). Pooling the crude ORs and adjusted ORs, showed that the relationship between opium use and GI cancer was statistically significant in both analyses with increased odds of 2.53 (95% CI of 1.95- 3.29, P<0.001, I2= 87.56%) and 2.64 (95% CI of 1.99- 3.51, P<0.001, I2= 78.51%). Besides, we performed separate quantitative analyses on the studies reporting the relationship between high daily use of opium, long duration of opium use and high cumulative use of opium, all compared to never use, and GI cancer. The statistical analyses showed that there were significant association between all of them and GI with ORs of 3.41 (95% CI of 1.92- 6.06, P<0.001, I2= 71.34), 3.03 (95% CI of 1.90- 4.84, P<0.001, I2= 80.28) and 3.88 (95% CI of 2.35- 6.41, P<0.001, I2= 68.87), respectively.

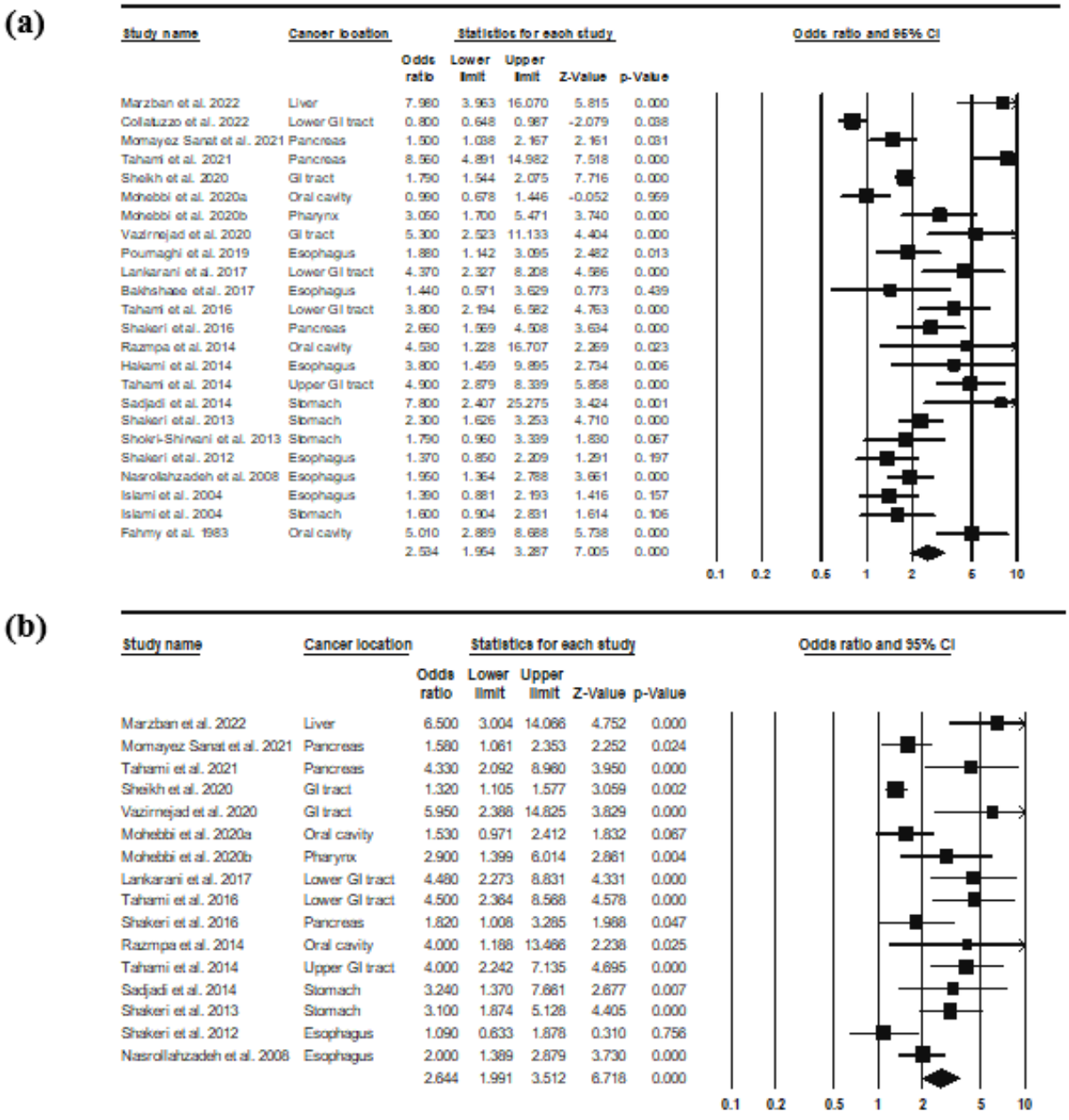
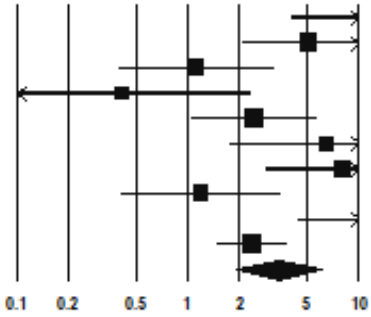


Figure 2. Forest plots of the individual and pooled (a) crude and (b) adjusted effect sizes of opium use and various GI cancers

Subgroup analyses was conducted to assess between the association between opium use and different GI cancers including oropharyngeal cancer, esophageal cancer, gastric cancer, pancreatic cancer, liver cancer, colorectal cancer, colon cancer and rectal cancer. The analyses found significant associations between opium use and oropharyngeal cancer (OR of 2.22 with 95% CI of 1.26- 3.90), gastric cancer (OR

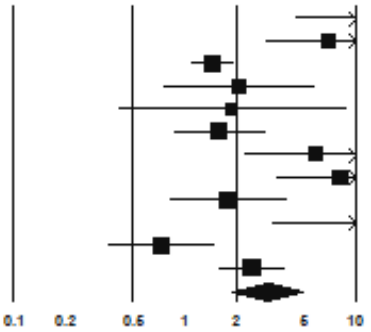
(a)

Study name	Cancer location	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Marzban et al. 2022	Liver	10.700	3.988	28.707	4.707	0.000
Tahami et al. 2021	Pancreas	5.100	2.103	12.368	3.605	0.000
Mohebbi et al. 2020	Oral cavity	1.120	0.392	3.203	0.211	0.833
Mohebbi et al. 2020	Pharynx	0.410	0.072	2.330	-1.006	0.314
Pournaghi et al. 2019	Esophagus	2.440	1.038	5.737	2.045	0.041
Lankarani et al. 2017	Lower GI tract	6.530	1.748	24.388	2.791	0.005
Tahami et al. 2016	Lower GI tract	8.000	2.841	22.526	3.937	0.000
Shakeri et al. 2016	Pancreas	1.190	0.407	3.482	0.318	0.751
Tahami et al. 2014	Upper GI tract	14.000	4.404	44.507	4.472	0.000
Nasrollahzadeh et al. 2008	Esophagus	2.380	1.471	3.852	3.530	0.000
		3.411	1.920	6.059	4.185	0.000



(b)

Study name	Cancer location	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Marzban et al. 2022	Liver	11.650	4.428	30.654	4.974	0.000
Tahami et al. 2021	Pancreas	6.980	3.011	16.183	4.529	0.000
Sheikh et al. 2020	GI tract	1.460	1.092	1.953	2.550	0.011
Mohebbi et al. 2020	Oral cavity	2.090	0.752	5.812	1.413	0.158
Mohebbi et al. 2020	Pharynx	1.900	0.410	8.810	0.820	0.412
Pournaghi et al. 2019	Esophagus	1.600	0.867	2.951	1.505	0.132
Lankarani et al. 2017	Lower GI tract	5.830	2.232	15.226	3.600	0.000
Tahami et al. 2016	Lower GI tract	8.100	3.418	19.194	4.752	0.000
Shakeri et al. 2016	Pancreas	1.790	0.809	3.963	1.436	0.151
Naghibzadeh Tahami et al. 2014	Upper GI tract	12.000	3.232	44.548	3.713	0.000
Shakeri et al. 2012	Esophagus	0.730	0.351	1.516	-0.844	0.399
Nasrollahzadeh et al. 2008	Esophagus	2.470	1.589	3.839	4.020	0.000
		3.032	1.899	4.840	4.647	0.000



(c)

Study name	Cancer location	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Marzban et al. 2022	Liver	11.000	3.831	31.586	4.455	0.000
Tahami et al. 2021	Pancreas	5.200	2.221	12.175	3.798	0.000
Mohebbi et al. 2020	Oral cavity	1.240	0.444	3.462	0.411	0.681
Mohebbi et al. 2020	Pharynx	1.070	0.223	5.142	0.084	0.933
Lankarani et al. 2017	Lower GI tract	4.630	1.779	12.047	3.141	0.002
Tahami et al. 2016	Lower GI tract	8.000	2.925	21.884	4.050	0.000
Shakeri et al. 2016	Pancreas	1.520	0.672	3.439	1.005	0.315
Tahami et al. 2014	Upper GI tract	18.700	5.512	63.440	4.699	0.000
Shakeri et al. 2013	Stomach	4.500	2.341	8.651	4.510	0.000
Nasrollahzadeh et al. 2008	Esophagus	2.340	1.449	3.778	3.478	0.001
		3.883	2.352	6.411	5.304	0.000

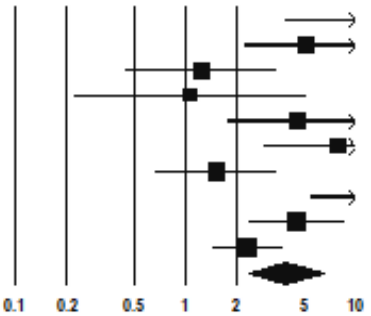


Figure 3. Forest plots of the individual and pooled effect sizes for the association of (a) high daily dose of opium use compared to never use and GI cancer (b) long duration of opium use compared to never use and GI cancer (c) high cumulative opium use compared to never use and GI cancer

of 3.09 with 95% CI of 2.16- 4.42), pancreatic cancer (OR of 2.17 with 95% CI of 1.25- 3.76), liver cancer (OR of 6.5 with 95% CI of 2.87- 13.44, only one study), colorectal cancer (OR of 4.49 with 95% CI of 2.81- 7.16) and colon cancer (OR of 5.58 with 95% CI of 3.14- 9.92) when considering only those adjusted effect sizes (Table 2). There was a significant relationship between opium use and esophageal cancer when including all studies, with either crude ORs or adjusted ORs, in the quantitative analysis (OR of 1.74 with 95% CI of 1.44- 2.10, P<0.001, I2= 18.36%). There were no adjusted effect sizes reported for sole rectal cancer in the studies; the pooled effect size was not significant (OR of 0.86 with 95% CI of 0.65- 1.13, P= 0.291, I2= 0.00%).

Sensitivity analysis

There were no significant differences in the results of any meta-analyses on the association of opium use, high daily use of opium, long duration of opium use and high cumulative use of opium following sensitivity analyses using "leave-one-out" of the studies. The plots of the sensitivity analyses are provided in Supplementary Figure 1.

Publication bias

The potential publication bias in this systematic review and meta-analysis for the associations of opium

Table 2. Subgroup analyses regarding the association between opium use and GI cancer

		Number of results	Pooled OR	95% CI	P value	I-squared	Q statistics p-value
Opium use and GI cancer							
Minimally adjusted studies		24	2.53	1.95- 3.29	<0.001	87.56	<0.001
Current opium use		8	2.39	1.61- 3.56	<0.001	67.32	0.003
Ever opium use		17	2.57	1.89- 3.51	<0.001	90.00	<0.001
Ever opium use in case-control studies		15	2.57	1.75- 3.75	<0.001	90.90	<0.001
Ever opium use in case-cohort studies		2	3.31	0.80- 13.75	0.099	83.13	0.015
Fully adjusted studies		16	2.64	1.99- 3.51	<0.001	78.51	<0.001
Current opium use		2	5.15	2.48- 10.69	<0.001	00.00	0.608
Ever opium use		14	2.49	1.87- 3.23	<0.001	79.08	<0.001
Ever opium use in case-control studies		14	2.78	2.09- 3.70	<0.001	69.37	<0.001
Ever opium use in case-cohort studies		2	1.87	0.79- 4.39	0.153	75.07	0.045
Oropharyngeal cancer	Overall	5	2.71	1.61- 4.57	<0.001	65.65	0.020
	Only adjusted studies	3	2.22	1.26- 3.90	0.006	44.02	0.168
Esophageal cancer	Overall	7	1.74	1.44- 2.10	<0.001	18.36	0.290
	Only adjusted studies	2	1.53	0.85- 2.76	0.159	69.72	0.069
Gastric cancer	Overall	6	2.21	1.80- 2.71	<0.001	9.52	0.355
	Only adjusted studies	3	3.09	2.16- 4.42	<0.001	00.00	0.990
Pancreatic cancer	Overall	4	2.05	1.42- 2.97	<0.001	47.81	0.124
	Only adjusted studies	3	2.17	1.25- 3.76	0.006	65.20	0.056
Liver cancer	Overall	2	3.35	0.98- 11.46	0.054	85.78	0.008
	Only adjusted studies	1	6.5	2.87- 13.44	<0.001	-	-
Colorectal cancer	Overall	3	2.46	0.63- 9.50	0.193	95.41	<0.001
	Only adjusted studies	2	4.49	2.81- 7.16	<0.001	00.00	0.993
Colon cancer	Overall	4	2.03	0.75- 5.50	0.165	91.98	<0.001
	Only adjusted studies	2	5.58	3.14- 9.92	<0.001	00.00	0.928
Rectal cancer	Overall (no adjusted studies)	2	0.86	0.65- 1.13	0.291	00.00	0.350
High daily use of opium compared to never use							
	Overall	10	3.41	1.92- 6.06	<0.001	71.34	<0.001
	Only adjusted studies	9	3.55	1.85- 6.79	<0.001	74.24	<0.001
	Esophagus	2	2.39	1.57- 3.64	<0.001	00.00	0.960
	Pancreas	2	2.55	0.613- 10.58	0.199	76.19	0.040
	Lower GI tract	2	7.40	3.28- 16.71	<0.001	00.00	0.812
	Colon cancer	2	8.86	3.67- 21.37	<0.001	00.00	0.840
Long duration of opium use compared to never use							
	Overall	12	3.03	1.90- 4.84	<0.001	80.28	<0.001
	Case-control studies	11	3.34	1.98- 5.64	<0.001	77.25	<0.001
	Only adjusted studies	11	3.27	1.95- 5.49	<0.001	81.73	<0.001
	Lower GI tract	2	6.99	3.68- 13.28	<0.001	00.00	0.618

Continuous							
	Esophagus	3	1.50	0.76- 2.94	0.242	74.75	0.019
	Pancreas	2	3.51	0.92- 13.31	0.065	81.18	0.021
	Colon	2	8.24	3.50- 19.38	<0.001	00.00	0.803
High cumulative use of opium compared to never use							
	Overall	10	3.88	2.35- 6.41	<0.001	68.87	0.001
	Stomach	2	5.20	2.90- 9.32	<0.001	00.00	0.336
	Pancreas	2	2.79	0.67- 3.44	0.095	76.03	0.041
	Lower GI tract	2	6.00	3.00- 12.00	<0.001	00.00	0.440
	Colon cancer	2	8.86	3.67- 21.37	<0.001	00.00	0.840
Ingestion of opium compared to never use							
	Overall	7	2.52	1.38- 4.59	0.002	69.17	0.003
	Case-control studies	6	3.51	1.55- 7.96	0.003	64.46	0.015
	Only adjusted studies	6	3.20	1.52- 6.74	0.002	74.00	0.002
	Esophagus	2	1.67	1.06- 2.62	0.027	00.00	0.428
Ingestion of opium compared to never use							
	Overall	7	1.95	1.36- 2.80	<0.001	70.83	0.002
	Case-control studies	6	2.19	1.44- 3.33	<0.001	61.85	0.022
	Only adjusted studies	6	1.91	1.27- 2.86	0.002	72.20	0.003
	Esophagus	2	1.91	1.35- 2.70	<0.001	00.00	0.370
Both smoking and ingestion of opium compared to never use							
	Overall	3	5.13	2.77- 5.21	<0.001	00.00	0.534
Teriak consumption compared to never use							
	Overall	6	2.15	1.45- 3.18	<0.001	76.56	0.001
	Case-control studies	5	2.50	1.53- 4.07	<0.001	70.71	0.008
Shireh consumption compared to never use							
	Overall	5	2.49	1.16- 5.34	0.019	63.91	0.026
	Case-control studies	4	3.52	1.96- 6.33	<0.001	00.00	0.900
Teriak and shireh consumption compared to never use							
	Overall	3	3.66	0.67- 20.10	0.135	80.91	0.005
	Case-control studies	2	8.74	2.83- 26.99	<0.001	00.00	0.985

use based on the crude effect sizes and adjusted effect sizes, high daily use of opium, long duration of opium use and high cumulative use of opium were assessed using Egger's test (Figure 3). The p-values of this test for these associations were 0.004, 0.0001, 0.748, 0.049 and 0.397, respectively; therefore, potential publication bias was seen for three analyses. For these studies, trim and fill analysis was conducted; however, the imputed studies did not change the significancy of the results in none of the analyses. The funnel plots of these analyses with and without imputed studies are presented in Figure 4 and Supplementary Figure 2.

Discussion

To the best of our knowledge, the current study is the most comprehensive systematic review and meta-analysis conducted to assess the relationship between use of opium and GI cancer. In our study, 22 articles with total population of 68546 participants and 5897 individuals with GI cancer were included compared to the two previous meta-analysis studies published in 2021 with 12 and 16 studies on the association of opium use and GI cancer (12, 13). There were significant relationships between opium use based on crude effect sizes and adjusted effect sizes, high daily opium use, long duration of opium use, high cumulative opium use, opium ingestion, opium smoking, teriak consumption and shireh consumption, all compared to never opium use, and GI cancer. The results were not sensitive to sensitivity analyses and no influential publication biases were found in these analyses.

The carcinogen effects of opium and its pyrolysates on different parts of the body have been reported in many studies (13). However, the present systematic review and meta-analysis specifically investigated the association between opium use and GI cancers. Opium is an extremely addictive substance that is extracted from the opium poppy. It is widely used for recreational purposes, especially in Middle Eastern countries. About 58 million individuals have been estimated to use opiates globally. These individuals are mostly from countries such as Iran, Pakistan, Afghanistan, India, and parts of Southeast Asia (40-42).

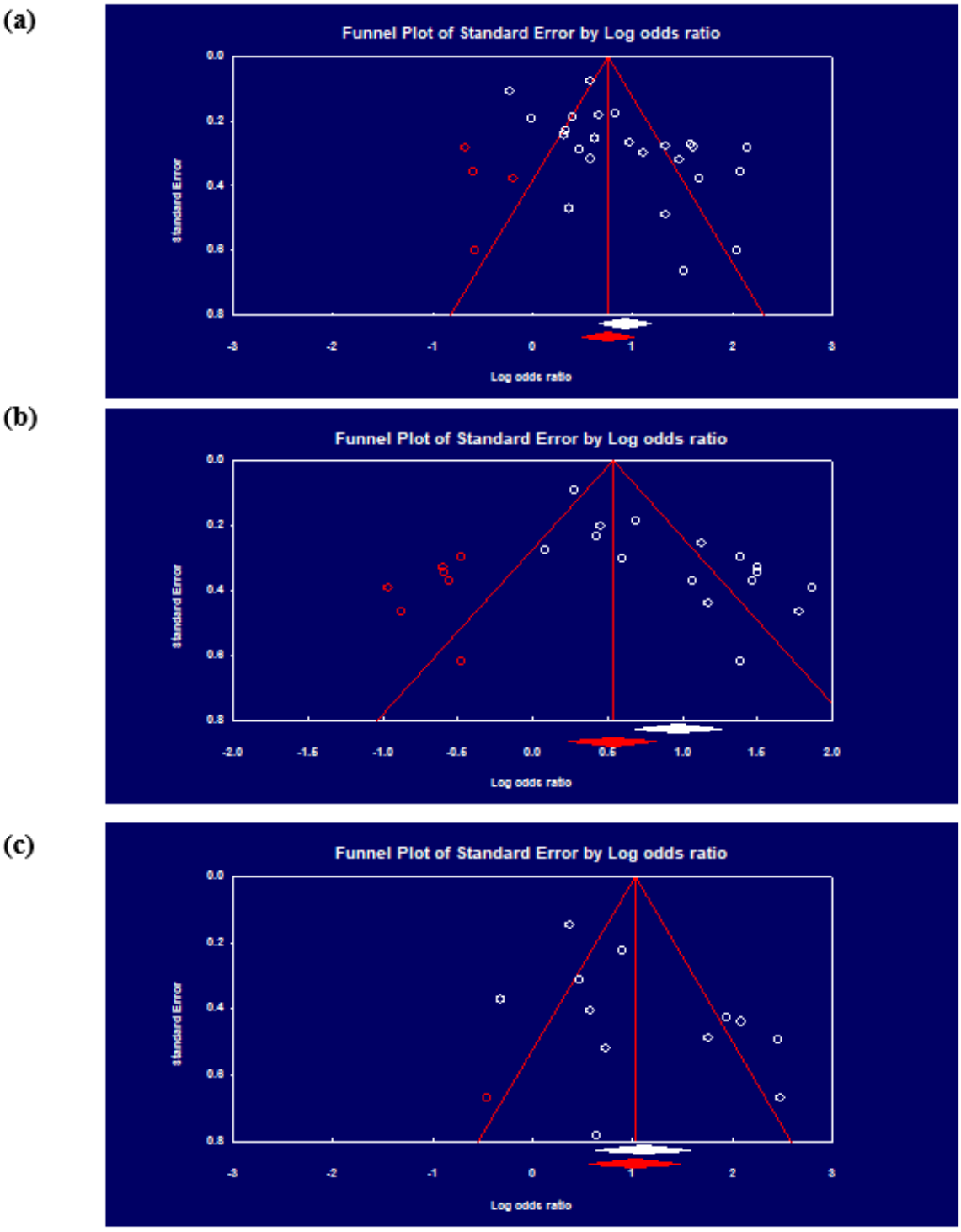


Figure 4. Funnel plots of observed studies and studies imputed by Trim and fill analysis on association of (a) opium use and GI cancer based on crude effect sizes (b) opium use and GI cancer based on adjusted effect sizes (c) long duration of opium use compared to never use and GI cancer

The pathophysiology of the association between opium use and GI cancers is not completely clear. Opium and some of its metabolites such as opium pyrolysis metabolites, morphine, and nitrosamines may play a role in this association. The genotoxic or mutagenic effect may be an explanation for this role

(10, 43-45). Nitrosamines are a known carcinogen in the GI tract (46). Morphine, a predominant alkaloid of opium, is a genotoxic opium metabolite through DNA methylation, inhibiting nitrosamines clearance (46-48). Opium pyrolysis produces heterocyclic and polycyclic aromatic hydrocarbons, primary aromatic amines, and N-nitrosamines that can induce dose-dependent mutations in bacteria, mammalian, and human cells (43-45, 48-51). Therefore, it seems that in addition to the mutagenic effect, there are other mechanisms to explain the carcinogenic effect of opium. Some of these mechanisms include the activation of angiogenesis and neovascularization (52, 53), increased cancer cell proliferation and migration (53), impairment of immune function (54), increased nitric oxide (55, 56), decreased hydrogen peroxide (56), and prolonged exposure of some organs to the carcinogens by impairment of their normal function (10).

It should be noted that this systematic review has some strengths. Firstly, the authors meticulously combed through various databases, such as PubMed, Embase, and Cochrane Library, to unearth studies of relevance. This meticulous approach substantially heightens the probability of encompassing all pertinent research and minimizes potential biases in selection. Secondly, the study incorporated a total of 21 case-control and cohort studies, amassing an aggregate sample size of approximately 70,000 participants. This sizable cohort markedly amplifies the study's statistical potency and fine-tunes its estimations' precision. Thirdly, the study's authors employed rigorous statistical techniques for data analysis, encompassing the application of random-effects models and the execution of sensitivity analyses. These methodologies serve to address disparities between studies and augment the dependability of the findings. Lastly, in this study we conducted the statistical analyses with both crude effect sizes and adjusted effect sizes. As cancer is a multifactorial disease, there may be lots of confounders which could affect the analyses when assessing the association between opium use and GI cancer, although the control groups of the included studies were nearly all at least matched with patients for age and sex. Besides, in many studies, the results were adjusted by place of residence, smoking or alcohol habits of the participants and their dietary intakes. Besides, the results of our study were not sensitive to leave-one-out of the included studies and they did not change following sensitivity analyses. Furthermore, although, Egger's test found potential publication biases for association of opium use in both crude model and adjusted model and long duration of opium versus never use of opium and GI cancer, the trim and fill analyses, showed the probable missing studies would not change the results significantly.

There were also limitations. The included studies were all observational, mainly with a case-control design; therefore, the results are subjected to recall bias. Recall bias is a recognized concern in studies reliant on self-reported information, especially when assessing past behaviors or exposures. In the context of our study, where opium use was evaluated through questionnaires, there exists a possibility that participants may not accurately recall or report their opium consumption. This can introduce a degree of measurement error and potentially lead to misclassification of exposure status. To address this concern, we took several measures to minimize the impact of recall bias. Firstly, we employed a standardized interview method across all participants, ensuring consistent and uniform data collection. Additionally, we ensured that the interviewers were well-trained, which can enhance the quality and reliability of the collected information. Despite these efforts, we acknowledge that some degree of under-reporting may still occur. This is an inherent challenge in studies of this nature, and we have duly noted this as a limitation in our research. In light of this, we suggest that future studies exploring the association between opium use and gastrointestinal cancer may consider employing complementary methods or validation techniques to corroborate self-reported data. Furthermore, conducting sensitivity analyses or employing statistical techniques that are robust to potential misclassification could be explored as strategies to assess the potential impact of under-reporting on our findings.

The studies encompassed in this analysis were predominantly observational, implying a potential susceptibility to the influence of extraneous variables. For instance, individuals using opium may exhibit other lifestyle or environmental traits that elevate their susceptibility to GI cancers, such as consuming other illicit substances, engaging in risky

sexual behaviors, suboptimal hygiene practices, and malnutrition. Regrettably, these factors were not factored into the analysis.

Moreover, the studies integrated into the analysis exhibited variability in how they defined and measured opium use. This diversity in approach may have introduced some degree of inconsistency in the findings. Additionally, details regarding the duration and frequency of opium use were not consistently reported across the studies, potentially impacting the strength of the observed association.

In any systematic review and meta-analysis, there exists a potential for publication bias. This arises from the tendency to favor the publication of studies with positive or significant findings, while those with null or negative results may be less likely to be disseminated or included in the analysis. Although the study authors made efforts to address this by means of a funnel plot analysis and Egger's test, the potential for bias cannot be entirely dismissed.

Future research directions

Some research directions are recommended to be pursued for elucidating more potential aspects of the association between opium and GI cancers. By embarking on research endeavors in these outlined directions, we envision a more comprehensive and nuanced understanding of the complex relationship between opium use and GI cancers, ultimately contributing to more effective prevention and intervention strategies.

Exploring Subtypes of GI Cancers: Future studies might delve deeper into specific subtypes of GI cancers to elucidate any nuanced associations with opium use. For example, focusing on esophageal adenocarcinoma, pancreatic neuroendocrine tumors, or colorectal adenomas could provide valuable insights into subtype-specific risks. Longitudinal Studies: Long-term cohort studies tracking opium users over extended periods could offer a clearer picture of the cumulative effects of opium exposure on GI cancer risk. Such studies would be instrumental in establishing temporal relationships and dose-response associations. Geographical Variations: Considering the potential impact of regional practices and differences in opium consumption patterns, a comparative analysis across diverse geographic regions could uncover variations in GI cancer risk associated with opium use. Impact on High-Risk Populations: Investigating the association within specific high-risk populations, such as those with genetic predispositions or pre-existing GI conditions, may yield critical insights into the interplay between opium use and genetic susceptibility. Behavioral Factors: Future research could delve into the potential mediating role of other behaviors associated with opium use, such as dietary patterns, smoking, or alcohol consumption, which may further influence GI cancer risk. Exploring Mechanistic Pathways: In-depth molecular and cellular studies could elucidate the underlying biological mechanisms linking opium use to the development of GI cancers. This could include investigating genetic mutations, epigenetic modifications, or alterations in cellular signaling pathways. Effect Modification by Demographics: Examining whether demographic factors such as age, gender, or socioeconomic status modify the association between opium use and GI cancers can provide a more nuanced understanding of population-specific risks. Intervention Studies: Evaluating the impact of interventions aimed at reducing or mitigating opium use on GI cancer incidence could offer critical insights into the potential benefits of harm reduction strategies.

Conclusion

Our meta-analysis showed that opium use could be strongly associated with increased risk of overall GI cancer and some particular GI cancers including oropharyngeal, gastric, pancreatic, colorectal, and colon cancers. For association of opium use and liver cancer, there were only one adjusted finding, although statistically significant; therefore, more studies are required to determine their association. In summary, the prevalence of opium use and also the incidence of GI cancers and thereby, its burden, are high in the world, particularly in Middle Eastern countries. Opium use as a potentially modifiable factor, therefore, should be more emphasized.

Conflict of interests

The authors declare no competing financial interests.

References

1. Cancer [https://www.who.int/news-room/fact-sheets/detail/cancer]

2. Mattiuzzi C, Lippi G. Current cancer epidemiology. J Epidemiol Glob Health 2019;9:217-222.

3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-249.

4. Onyoh EF, Hsu WF, Chang LC, Lee YC, Wu MS, Chiu HM. The rise of colorectal cancer in Asia: epidemiology, screening, and management. Curr Gastroenterol Rep 2019;21:1-10.

5. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017;66:683-691.

6. Huang FL, Yu SJ. Esophageal cancer: risk factors, genetic association, and treatment. Asian J Surg 2018;41:210-215.

7. Murphy N, Jenab M, Gunter MJ. Adiposity and gastrointestinal cancers: epidemiology, mechanisms and future directions. Nat Rev Gastroenterol Hepatol 2 018;15:659-670.

8. Ocvirk S, Wilson AS, Appolonia CN, Thomas TK, O'Keefe SJ. Fiber, fat, and colorectal cancer: new insight into modifiable dietary risk factors. Curr Gastroenterol Rep 2019;21:1-7.

9. Cook-Mozaffari P, Azordegan F, Day N, Ressicaud A, Sabai C, Aramesh B. Oesophageal cancer studies in the Caspian Littoral of Iran: results of a case-control study. Br J Cancer 1979;39:293-309.

10. Sheikh M, Shakeri R, Poustchi H, Pourshams A, Etemadi A, Islami F, et al. Opium use and subsequent incidence of cancer: results from the Golestan Cohort Study. Lancet Glob Health 2020;8:649-660.

11. Rashidian H, Zendehdel K, Kamangar F, Malekzadeh R, Haghdoost AA. An ecological study of the association between opiate use and incidence of cancers. Addiction & Health 2016;8:252.

12. Mansouri M, Naghshi S, Parsaeian M, G Sepanlou S, Poustchi H, Momayez Sanat Z, et al. Opium use and cancer risk: a comprehensive systematic review and meta-analysis of observational studies. Int J Clin Pract 2022;2022:5397449.

13. Bidary MZ, Sahranavard M, Rezayat AA, Omranzadeh A, Hoseiny SH, Kabirian A, et al. Opium as a carcinogen: a systematic review and meta-analysis. EClinicalMedicine 2021;33:100768.

14. Shokri-Shirvani J, Kordinejad B, Meftah N, Amani N. Demographic characteristics, clinical symptoms and endoscopic findings in patients with gastric ulcer versus gastric cancer. J Babol Univ Med Sci 2013;15:59-64.

15. Pournaghi SJ, Hojjat SK, Barazandeh Noveyri F, Tavakkoli Ghouchani H, Ahmadi A, Hamedi A, et al. Tobacco consumption, opium use, alcohol drinking and the risk of esophageal cancer in North Khorasan, Iran. J Subst Use 2019;24:105-109.

16. Islami F, Kamangar F, Aghcheli K, Fahimi S, Semnani S, Taghavi N, et al. Epidemiologic features of upper gastrointestinal tract cancers in Northeastern Iran. Br J Cancer 2004;90:1402-1406.

17. Collatuzzo G, Seyyedsalehi MS, Rezaeianzadeh A, Marzban M, Rashidian H, Hadji M, et al. Consumption of yoghurt and other dairy products and risk of colorectal cancer in Iran: the IROPICAN study. Nutrients 2022;14.

18. Marzban M, Mohebbi E, Haghdoost A, Aryaie M, Zahedi MJ, Khazaei Z, et al. Opium use and the risk of liver cancer: a case-control study. Cancer Prev Res 2023;16:29-35.

19. Momayez Sanat Z, Masoudi S, Mansouri M, Ghamarzad Shishavan N, Jameshorani M, Pourshams A. Diabetes mellitus, obesity, and risk of pancreatic ductal adenocarcinoma: a large case-control study from Iran. Middle East J Dig Dis 2021;13:15-20.

20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Br Med J 2021;372:71.

21. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-605.

22. Marzban M, Mohebbi E, Haghdoost A, Aryaie M, Zahedi MJ, Khazaei Z, et al. Opium use and the risk of liver cancer: a case-control study. Cancer Prev Res 2023;16:29-35.

23. Naghibzadeh-Tahami A, Marzban M, Yazdi-Feyzabadi V, Khazaei Z, Zahedi MJ, Moazed V, et al. Opium use as an independent risk factor for pancreatic cancer: a case-control study. Cancer Epidemiol 2021;75:102017.

24. Mohebbi E, Hadji M, Rashidian H, Rezaianzadeh A, Marzban M, Haghdoost AA, et al. Opium use and the risk of head and neck squamous cell carcinoma. Int J Cancer 2021;148:1066-1076.

25. Sheikh M, Shakeri R, Poustchi H, Pourshams A, Etemadi A, Islami F, et al. Opium use and subsequent incidence of cancer: results from the Golestan Cohort Study. Lancet Global Health 2020;8:649-660.

26. Vazirinejad R, Najafipour R, Rezaeian M, Ghazizadeh A, Doost Mohammadi F. Opium and risk of gastrointestinal cancer: a case-control study. Turk J Med Sci 2020;50:697-705.

27. Lankarani KB, Khosravizadegan Z, Naghibzadeh-Tahami A, Akbari M, Khodadost M, Honarvar B, et al. Opium use and risk of lower gastrointestinal cancers: population-based case-control study in south of Iran. Int J Cancer Manag 2017;10:8227.

28. Bakhshaee M, Raziee HR, Afshari R, Amali A, Roopoosh M, Lotfizadeh A. Opium addiction and risk of laryngeal and esophageal carcinoma. Iran J Otorhinolaryngol 2017;29:19-22.

29. Shakeri R, Kamangar F, Mohamadnejad M, Tabrizi R, Zamani F, Mohamadkhani A, et al Opium use, cigarette smoking, and alcohol consumption in relation to pancreatic cancer. Medicine 2016;95:3922.

30. Ahmad NT, Vahid YF, Narges K, Ahad AA, Hosniyeh A, Vahid Reza B, 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.

31. Razmpa E, Saedi B, Motiee-langroudi M, Garajei A, Hoseinpor S, Motamedi MH. Opium usage as an etiologic factor of oral cavity cancer. J Craniofac Surg 2014;25:505-507.

32. Hakami R, Etemadi A, Kamangar F, Pourshams A, Mohtadinia J, Firoozi MS, et al. Cooking methods and esophageal squamous cell carcinoma in high-risk areas of Iran. Nutr Cancer 2014;66:500-505.

33. Naghibzadeh Tahami A, Khanjani N, Yazdi Feyzabadi V, Varzandeh M, Haghdoost AA. Opium as a risk factor for upper gastrointestinal cancers: a population-based case-control study in Iran. Arch Iran Med 2014;17:2-6.

34. Sadjadi A, Derakhshan MH, Yazdanbod A, Boreiri M, Parsaeian M, Babaei M, et al. Neglected role of hookah and opium in gastric carcinogenesis: a cohort study on risk factors and attributable fractions. Int J Cancer 2014;134:181-188.

35. Shakeri R, Malekzadeh R, Etemadi A, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, et al. Opium: an emerging risk factor for gastric adenocarcinoma. Int J Cancer 2013;133:455-461.

36. Shokri-Shirvani J, Kordinejad B, Meftah N, Amani N. Demographic characteristics, clinical symptoms and endoscopic findings in patients with gastric ulcer versus gastric cancer. J Babol Univ Med Sci 2013;15:59-64.

37. Shakeri R, Kamangar F, Nasrollahzadeh D, Nouraie M, Khademi H, Etemadi A, et al. Is opium a real risk factor for esophageal cancer or just a methodological artifact? Hospital and neighborhood controls in case-control studies. PloS one 2012;7:32711.

38. Nasrollahzadeh D, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet CC, et al. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. Br J Cancer 2008;98:1857-1863.

39. Fahmy MS, Sadeghi A, Behmard S. Epidemiologic study of oral cancer in Fars Province, Iran. Community Dent Oral Epidemiol 1983;11:50-58.

40. Shakeri R, Malekzadeh R, Etemadi A, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, et al. Opium: an emerging risk factor for gastric adenocarcinoma. Int J Cancer 2013;133:455-461.

41. Nakhaee N, Divsalar K, Meimandi MS, Dabiri S. Estimating the prevalence of opiates use by unlinked anonymous urine drug testing: a pilot study in Iran. Subst Use Misuse 2008;43:513-520.

42. Zarghami M. Iranian common attitude toward opium consumption. Iran J Psychiatry Behav Sci 2015;9.

43. Masjedi MR, Naghan PA, Taslimi S, Yousefifard M, Ebrahimi SM, Khosravi A, et al. Opium could be considered an independent risk factor for lung cancer: a case-control study. Respiration 2013;85:112-118.

44. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol 2015;44:186-198.

45. Lucenteforte E, La Vecchia C, Silverman D, Petersen G, Bracci P, Ji Ba, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case–Control Consortium (PanC4). Ann Oncol 2012;23:374-382.

46. Ribeiro Pinto L, Swann PF. Opium and oesophageal cancer: effect of morphine and opium on the metabolism of N-nitrosodimethylamine and N-nitrosodiethylamine in the rat. Carcinogenesis 1997;18:365-369.

47. Hosseini SY, Safarinejad MR, Amini E, Hooshyar H. Opium consumption and risk of bladder cancer: a case-control analysis. In: Urologic Oncology: Seminars and Original Investigations: 2010: Elsevier; 2010: 610-616.

48. Friesen M, O'neill IK, Malaveille C, Garren L, Hautefeuille A, Bartsch H. Substituted hydroxyphenanthrenes in opium pyrolysates implicated in oesophageal cancer in Iran: structures and in vitro metabolic activation of a novel class of mutagens. Carcinogenesis 1987;8:1423-1432.

49. Zou L, Zhong R, Shen N, Chen W, Zhu B, Ke J, et al. Non-linear dose–response relationship between cigarette smoking and pancreatic cancer risk: evidence from a meta-analysis of 42 observational studies. Eur J Cancer 2014;50:193-203.

50. Hewer T, Rose E, Ghadirian P, Castegnaro M, Malaveille C, Bartsch H, Day N. Ingested mutagens

from opium and tobacco pyrolysis products and cancer of the oesophagus. Lancet 1978;312:494-496.

51. Perry P, Thomson E, Day N, Bartsch H. Induction of SCE by opium pyrolysates in CHO cells and human peripheral blood lymphocytes. Carcinogenesis 1983;4:227-230.

52. Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: a review. Am J Ther 2004;11:354-365.

53. Bosetti C, Lucenteforte E, Silverman D, Petersen G, Bracci P, Ji B, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol 2012;23:1880-1888.

54. Kamangar F, Malekzadeh R, Dawsey SM, Saeidi F. Esophageal cancer in Northeastern Iran: a review. Arch Iran Med 2007;10:70-82.

55. Fimiani C, Arcuri E, Santoni A, Rialas C, Bilfinger T, Peter D, et al. μ3 Opiate receptor expression in lung and lung carcinoma: ligand binding and coupling to nitric oxide release. Cancer letters 1999;146:45-51.

56. Bosshart H. Morphine and cancer progression: hydrogen peroxide points to need for more research. J. Opioid Manag 2011;7:93-96.