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The significant impact of opium use on various types of cancer: an updated - systematic review and meta-analysis

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Abstract

Objective The existing literature on the direct effects of opioid use on cancer is limited. The goal of our systematic review and meta-analysis is to consolidate the findings of previous studies and provide a pooled effect size regarding the association between opioid usage and cancer.

Methods The PRISMA guidelines were employed to construct a framework for conducting this systematic review and meta-analysis. A systematic search was conducted in international and national databases. A search of PubMed, Web of Science, Scopus, and national electronic databases was conducted up to May 2024. The random effects model was employed for the presentation of results with a 95% confidence interval. The statistical analysis was conducted using Stata 11.

Results Out of 1674 articles were retrieved 38 studies remained in the final analysis (six cohort study and 32 case-control studies). The pooled adjusted odds ratio of opium on esophageal cancer was 1.68 (95% CI: 1.36, 2.08), for bladder cancer was 5.00(95% CI: 3.76, 6.66), for head and neck cancer was 4.93 (95% CI: 2.41, 10.06) for pancreatic cancer was 2.4 (95% CI: 1.62, 2.56) for lung cancer was 2.89(95% CI: 2.14, 3.30) for laryngeal cancer was 6.76 (95% CI: 3.77, 11.80) for gastric cancer was 3.13 (95% CI: 1.92, 5.11) and for colorectal cancer was 2.51 (95% CI: 1.04, 6.07).All association were statistically significant.

Conclusion The findings underscore the potential carcinogenic effects of opium on cancers. Public health organizations should work collaboratively to mitigate opioid exposure while promoting alternative pain management strategies to protect community health and reduce the burden of cancer.

Keywords Opium, Neoplasms, Systematic review, Meta-Analysis

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Background

Opium has a longstanding history of medicinal and recreational use, primarily known for its pain-relieving and psychoactive effects [1]. Recent research indicates a complicated relationship between opium consumption and cancer risk, suggesting that opium may contribute to various health issues, especially cancer [2–5].

Opium and its components have been linked to a higher risk of cancer through various carcinogenic processes. Prolonged exposure to opium can lead to the production of reactive oxygen species, resulting in oxidative stress and DNA damage, which may trigger cancer development [6]. Additionally, opium is known to weaken the immune system, impairing the body's ability to identify and eliminate cancer cells. Its connection to tobacco use, especially in specific cultural contexts, further enhances its cancer-causing potential. Research indicates that opium metabolites like morphine and codeine may also affect cellular pathways that regulate cell growth and programmed cell death, potentially facilitating tumor formation. Together, these elements contribute to an elevated risk of several types of cancer, including lung, esophageal, and bladder cancers [7].

The prevalence of cancer linked to opium use is particularly pronounced in regions with high consumption, including parts of Asia, the Middle East, and North Africa, where elevated rates of lung, oral, and gastrointestinal cancers are observed [7, 8]. This emphasizes the importance of thorough studies on opium's impact on cancer risk and the creation of targeted public health strategies.

The consumption of opium is considered an additional risk factor for the onset of esophageal cancer [9]. In Iran, the rate of opium addiction has surged three times in the last twenty years, now ranging between 2% and 8.2%. It is estimated that around 7–8% of cases of drug-related health issues are reported in primary care facilities [10, 11]. Opium, which is part of opiate substances, has been associated with an increased risk of multiple types of cancer, such as esophageal [12], pancreatic [13], stomach [14, 15], bladder [16], lung [17, 18], and laryngeal [19, 20] cancers. The International Agency for Research on Cancer (IARC) has classified opium use as a Group I carcinogen [21].

The objective of this systematic review and meta-analysis is to consolidate previous analytical studies on the relationship between opium use and cancers, identifying which cancers are most significantly affected. The outcomes could guide health policies and interventions aimed at reducing cancer rates in populations with high opium use, ultimately enhancing public health outcomes. Understanding the connection between opium consumption and cancer development is crucial for effective prevention and treatment strategies in light of growing global health challenges.

Methods

This review has been prepared in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline.

Search strategy

A search was conducted on international databases, including PubMed, Web of Science, Scopus and Google Scholar up to May 28, 2024, without any restrictions on time or language. The reference lists of the studies were checked, and those articles were also reviewed. The search was performed using keywords such as: ("cancer/s", OR " malignancy/ies ", OR " neoplasm/s", OR " tumor/s"), AND ("opioid" OR "opium."(.

Eligibility criteria

In this systematic review, we focused on analytical observational studies, including analytical cross-sectional, case-control, and cohort designs, that explored the link between opium use and cancer risk. We included studies that supplied sufficient data to calculate effect sizes such as relative risk or odds ratios. The main outcome of this review is the incidence of esophageal cancer, which must be confirmed through pathological methods or medical assessments, with cancer classifications validated according to the International Classification of Diseases (ICD-10) standards.

The review's study population consists of individuals at risk for various cancer types, without limitations concerning country, age, gender, or ethnicity. While the primary attention is on esophageal cancer, its diagnosis and classification must comply with ICD-10 criteria. Additionally, there were no restrictions on the publication dates, geographical areas, or languages of the studies included, ensuring a thorough incorporation of pertinent research.

Study selection

After conducting a search in various databases, the results were transferred to EndNote software, which aided in eliminating duplicate entries. Two researchers were tasked with independently screening the titles and abstracts of the studies identified. Any disagreements between them were resolved through discussion, with the involvement of a third investigator when necessary. To evaluate their level of agreement, the kappa index was calculated and resulted in a value of 0.88, indicating a high level of consensus.

To gain a deeper understanding, the full texts of the selected studies were downloaded. Ultimately, studies

that fulfilled the inclusion criteria were incorporated into the review.

Data extraction

After a comprehensive review of the full texts of eligible studies, pertinent information was extracted and documented in a pre-designed datasheet. The extracted data encompassed several key elements: the first author's name, publication year, study location (country), average age of participants, gender distribution, total sample size, both crude and adjusted odds ratios, the upper and lower limits of the odds ratios, the adjusted factors considered in the statistical models, and the number of cases and controls in both exposed and non-exposed groups.

This collected data aims to facilitate further analysis and evaluation of the findings from the included studies. By leveraging this information, detailed reports can be created, providing a thorough understanding of the association between opium use and cancer risk.

Risk of bias assessment

To assess the quality of the studies included in this review, we utilized the Newcastle-Ottawa Scale (NOS). The specific criteria for quality evaluation included: (1) Outcome assessment; (2) Exposure ascertainment; (3) Definition and selection of controls; and (4) Reporting precision for the outcome (95% confidence interval). This assessment scale evaluates the quality and potential bias of the studies, with a maximum of nine stars assigned. Studies receiving seven stars or more are considered high quality.

The overall certainty of evidence across studies was evaluated using the grading of recommendations, assessment, development, and evaluations (GRADE) framework, as described by the GRADE Working Group [22]. This assessment categorized the certainty of evidence into four levels: high [4], moderate [3], low [2], and very low.These ratings indicate the confidence in the accuracy of the effect estimates [23]. According to GRADE criteria, factors that may lead to a lower certainty rating include risk of bias, inconsistency, indirectness, imprecision, and publication bias. Conversely, certainty can be increased due to factors such as a large effect size, a clear dose-response relationship, and the adjustment for all plausible residual confounding [23].

Heterogeneity and publication bias

We evaluated statistical heterogeneity by employing the chi-square test with a significance threshold of 10%. To further quantify heterogeneity, we calculated the I^2 statistic. The variance between studies was estimated using tau-squared (τ^2). To address the identified heterogeneity, we implemented the following strategies: (1) a thorough review of the extracted data; and (2) the application of a random effects model. Additionally, we visually assessed publication bias with a funnel plot and conducted Egger's tests at a significance level of 0.05 for statistical confirmation of publication bias.

Data synthesis

The standard error of adjusted odds ratios (OR) were with the following formula:

$$Standard\ Error\ of\ Ln\,(OR) = \frac{ln\,(upper\ limit\ of\ OR) - ln\,(lower\ limit\ of\ OR)}{2 \times\ 1.96} \quad (1)$$

The inverse variance method was employed to derive the odds ratios. The results were reported using a random effects model with a 95% confidence interval. The data were analyzed using Stata 11 (Stata Corp, College Station, TX, USA) at a 95% confidence interval.

Results

After conducting a thorough search of databases such as PubMed, Scopus, and Web of Science up until May 28th, we identified a total of 1907 articles. Among these, 356 were duplicates, and 1129 articles were excluded after screening their titles and abstracts. We then re-evaluated 422 articles, ultimately excluding 384 that did not meet the inclusion criteria or lacked full-text access. Finally, we included six cohort studies [4, 15, 24–26] and 32 case-control studies [3–5, 7, 12–14, 18, 19, 27–49] which collectively had a sample size 523,827 persons with mean age 56.58 ± 11.32 (Fig. 1; Table 1).

Synthesis of results

All of included studies have been conducted in Asian regions, especially in Iran. The analysis included one cohort study and ten case-control studies. Among the case-control studies, one study conducted by the same research team in a specific region compared the results of two different studies. Both studies used the same case definition, but they employed different control groups.

Heterogeneity and publication bias

To evaluate both quantitative and qualitative heterogeneity among the studies, the I^2 and Chi^2 tests were employed, with a significance level set at 0.05. Additionally, the tau-squared test was used to estimate the variances across the studies. Overall, a moderate level of heterogeneity (72.4%) was observed. The Cochrane test ($P < 0.05$) further confirmed that these inconsistencies were statistically significant.

In assessing publication bias, the distribution of studies was examined visually. The studies appeared to be distributed nearly symmetrically on both sides of the vertical line, indicating an absence of publication bias for

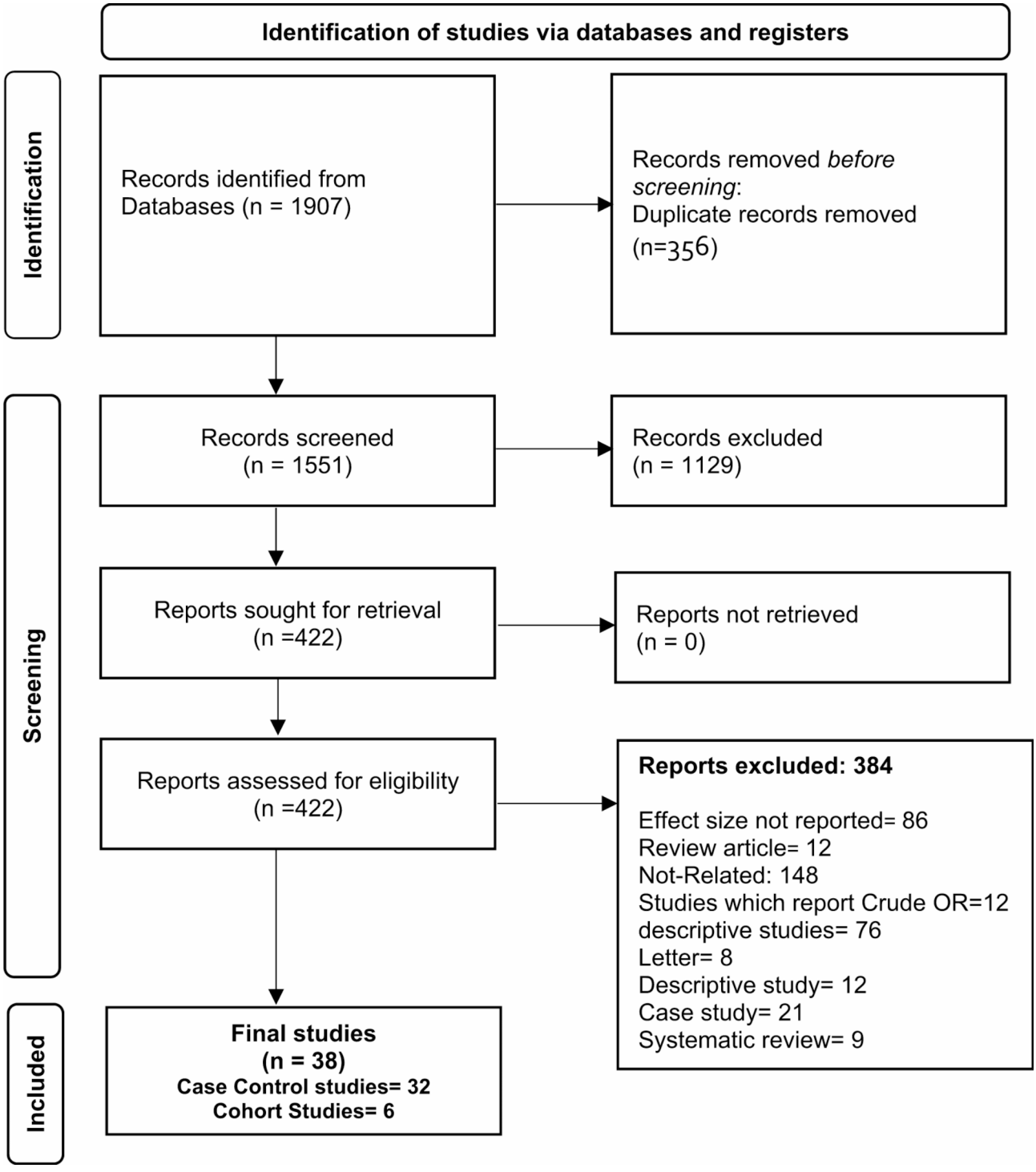

Fig. 1 A flow diagram depicting the phases of retrieving articles, checking eligibility criteria, and including the articles into the meta-analysis

five types of cancer: esophageal, pancreatic, lung, laryngeal, and gastric cancers.

The results of the publication bias assessment and sensitivity analysis using the Trim and Fill method reveal varying degrees of bias across different cancer types. For bladder cancer, the p-value was 0.567, indicating no significant publication bias, with an odds ratio (OR) of 5.003 (95% CI: 3.76–6.66) remaining unchanged when accounting for imputed studies. In esophageal cancer, the p-value of 0.064 suggests a potential for bias, leading to a slight decrease in the OR from 1.684 (95% CI: 1.36–2.08) to 1.61 (95% CI: 1.32–1.97) after imputation. Pancreatic

Table 1 The characteristics of included studies

Author	Cancer Type	Design	Mean age	Sample	City	Quality	Adjusted factors
Hosseini 2010	Bladder	Case-Control	NR	358	Tehran	Good	age, sex, smoking status, and family history of cancer
Ketabchi 2005	Bladder	Case-Control	NR		Kerman	Weak	age, gender, province, cigarette pack-years
Akbari 2015	Bladder	Case-Control	NR	594	Shiraz	Good	age, sex, residence, red meat, poultry, fish, hydrogenated oil, olive oil, butter intake, fat intake, fruit, nuts consumption, moldy foods, alcohol, tobacco use
Sadeghi 1979	Bladder	Case-Control	NR		Shiraz	Weak	age, sex
Nourbakhsh 2006	Bladder	Case-Control	NR		Tehran	Good	no history or presenting signs or symptoms of urinary problems, sex and age, cigarette smoking habits
Abdolahinia 2021	Bladder	Case-Control	63.6	300	Kerman	Moderate	age, sex, Socio-demographics status, occupational exposures, common diet, history of drug use and family history of cancer
Hadji 2022	Bladder	Case-Control	57.4		IROPICAN	Good	age, gender, place of residence and pack-years of cigarette smoking
Ghadimi 2015	Bladder	Case-Control	62.7	304	Kurdistan	Moderate	Smoking, sex, and place of residency, age (± 5 years)
Shakhssalim 2010	Bladder	Case-Control	64.67	19,384	Isfahan and East Azarbayjan	Good	gender and age (± 5 years), cigarette smoking
Asgari 2004	Bladder	Case-Control	61.2	160	Tehran	Weak	Sex
Behmorad 1981	Bladder	Case-Control			Shiraz	Moderate	age, gender, cigarette, smoking
Sheikh 2020	Bladder and Esophageal /lung	Cohort	52.1	50,045	Golestan	Good	sex, ethnicity (Turkman vs. non-Turkman), residence (urban vs. rural), wealth score quartiles, smoking cigarettes (ever vs. never), cumulative pack-years of smoked cigarettes, regular alcohol drinking (ever vs. never)
lankarani 2017	Colorectal	Case-Control	NR	480	Shiraz	Good	age and gender, residence, use of meat, fruit, vegetables hydrogenated fats, smoking
Naghibzadeh Tahami 2016	Colorectal	Case-Control	NR	525	Kerman	Good	age, sex, and place of residence, use of meat, fruit and vegetables, hydrogenated fats, cigarette
Hadji 2023	Colorectal	Case-Control	57.4	4043	IROPICAN	Good	age, gender, province, marital status, family history of cancer, red meat, vegetables, body shape, socioeconomic status, and perceived physical workload
Nasrollahzadeh 2008	Esophageal	Case-Control	64.4	871	Golestan	Moderate	residence, age (± 2 years), and sex, education and ethnicity
Pournaghi 2019	Esophageal	Case-Control	NR	283	North Khorasan	Weak	age and sex
Hakami 2014	Esophageal	Case-Control	62.5	120	Golestan	Moderate	smoking, opium use, rural residence, ethnicity and education
Sepehr 2005	Esophageal	Case-Control	NR	174	Golestan	Good	age, sex, and ethnic origin
Shakeri 2012	Esophageal	Case-Control	NR	390	Golestan	Good	age, sex, nass, hookah, ethnicity, education and place of residence
Sadjadi 2014	Gastric	Cohort	NR	9096	Ardabil	Good	gender, Family history of cancer smoking, Hookah smoking, Alcohol use, Fruit/veg. intake, Salt intake > 6 gr/day
Shakeri 2013	Gastric	Case-Control	63	309	Golestan	Good	age, ethnicity, education, fruit consumption, vegetable consumption, socioeconomic status, and in each case for the other three main variables cigarette, hookah and nass use

Table 1 (continued)

Author	Cancer Type	Design	Mean age	Sample	City	Quality	Adjusted factors
Vazirinejad 2020	Gastric	Case-Control	61.5	285	Rafsanjan	Good	education level, family history of cancer, consumption of red meat, fruit and vegetables
Naghibzadeh Tahami 2014	Gastric	Case-Control	62.21	390	Kerman	Moderate	age, sex, and place of residency
Mousavi 2003	Laryngeal	Case-Control	55.1	410	Kerman	Weak	age, sex, smoking
Bakhshaee 2017	Laryngeal	Case-Control	58.44	180	Mashhad	Weak	age, smoking
Mohebbi 2020	Laryngeal /Head and Neck	Case-Control	9.13	3698	IROPACAN	Good	age, gender, place of residence, pack-years of cigarette smoking, head-years of water-pipe smoking, regular alcohol drinking, socioeconomic status and oral health
Alizadeh 2020	Laryngeal and Head and Neck	Case-Control	NR	420	Kerman	Moderate	age, gender, and place of residence, use of meat, fruit and vegetables, hydrogenated fats, olive oil as well as levels of education
Marzban 2022	Liver	Case-Control	62.7	351	Kerman	Good	Age, gender, education, marital status, cigarette smoking
Rashidian 2023	Lung	Case-Control	NR*	4104	Multi Center	Good	age, gender, province, socioeconomic status, cigarette and water pipe use
Khademi 2012	Lung	Cohort	52.1	50,045	Gonabad	Good	sex, place of residence (urban or rural), marital status, highest educational level, ethnicity (Turkmen or others), and cigarette smoking
Masjedi 2011	Lung	Case-Control	59	726	Tehran	Moderate	age, gender, and place of residence, educational, ethnicity
Naghibzadeh-Tahami 2020	Lung	Case-Control	NR	420	Kerman	Good	age, gender, and place of residence, tobacco smoking, education, daily intake of fruit, vegetables, red meat, and hydrogenated fats
Shakeri 2016	Pancreatic	Case-Control	68.5	685	Tehran	Good	age, sex, place of residence (urban or rural), and mutual consumption of opium use, smoking, and alcohol consumption
Moossavi 2017	Pancreatic	Cohort	52.1	50,045	Golestan	Good	age, sex, cigarette smoking (never, Former, or current use), alcohol consumption, BMI, and diabetes mellitus
Barlass 2021	Pancreatic	Cohort	NR	70,300	USA	Weak	Age, BMI, Hight, Weight, Alcohol use
Naghibzadeh-Tahami 2021	Pancreatic	Case-Control	NR		Kerman	Moderate	age, sex, and place of residence, smoking
Sheikh 2020	Pancreatic /Pancreatic /Gastric	Cohort	NR	50,045	Golestan	Good	sex, ethnicity (Turkman vs. non-Turkman), residence (urban vs. rural), wealth score quartiles, smoking cigarettes, cumulative pack-years of smoked cigarettes and regular alcohol drinking

*: All studies were done in Iran. NR: Not Reported

cancer showed a significant p-value of 0.010, indicating publication bias, with the OR dropping from 2.04 (95% CI: 1.62–2.56) to 1.77 (95% CI: 1.28–2.44) when imputed studies were included. Conversely, lung cancer had a p-value of 0.454 and a stable OR of 2.89 (95% CI: 2.14–3.90), which decreased slightly to 2.745 (95% CI: 2.02–3.74) for imputed studies. Laryngeal cancer demonstrated a high p-value of 0.943 with an unchanged OR of 6.67 (95% CI: 3.77–11.80), suggesting no publication bias. Gastric cancer had a p-value of 0.803, with a notable drop in the OR from 3.13 (95% CI: 1.92–5.11) to 2.21 (95% CI: 1.30–3.77) upon imputation. Lastly, colorectal cancer's p-value of 0.186 indicated no significant bias, as its OR remained stable at 2.51 (95% CI: 1.04–6.07) across both observed and imputed studies. Overall, these findings highlight the importance of considering publication bias when interpreting the results of studies across various cancer types (Fig. 2 and Table 2).

Risk of bias assessment

In the current study, 57.14% of studies ($n = 22$), had good reporting quality, while 23.81% studies ($n = 10$), had moderate quality, and 16.67% ($n = 6$) had low quality (Tables 1 and 3).

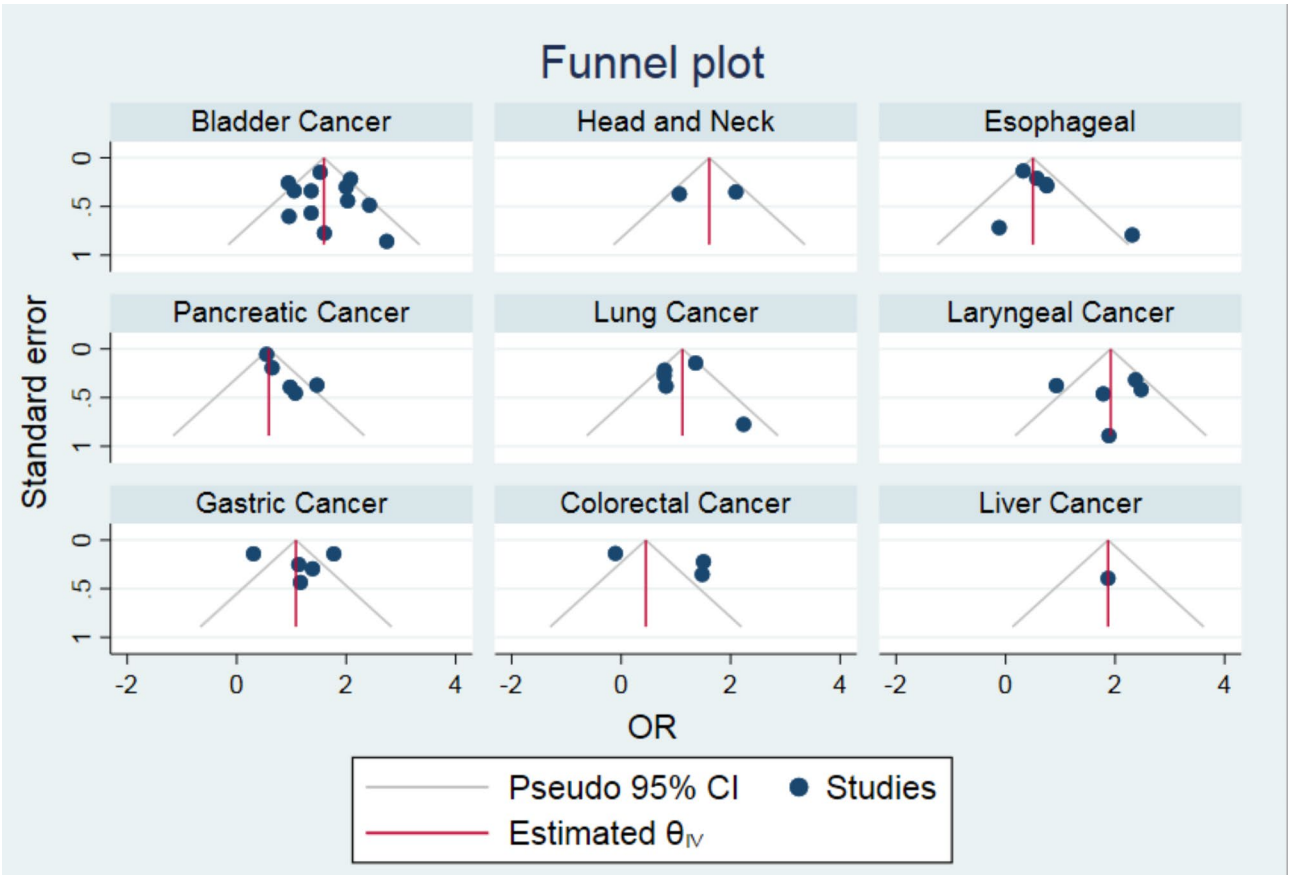

Fig. 2 A: Funnel plot of included studies by cancer type

Table 2 Publication Bias assessment and sensitivity analysis (Trim and Fill)

Cancer Type	*p*-value*	Observed Studies OR (95% CI)	Observed + imputed Studies OR (95% CI)
Bladder	0.567	5.00 (3.76, 6.66)	5.003 (3.76, 6.66)
Esophageal	0.064	1.68 (1.36, 2.08)	1.61 (1.32, 1.97)
Pancreatic	0.010	2.04 (1.62, 2.56)	1.77 (1.28, 2.44)
Lung	0.454	2.89 (2.14, 3.90)	2.745 (2.02, 3.74)
Laryngeal	0.943	6.67 (3.77, 11.80)	6.67 (3.77, 11.80)
Gastric	0.803	3.13 (1.92, 5.11)	2.21 (1.30, 3.77)
Colorectal	0.186	2.51(1.04, 6.07)	2.51 (1.04, 6.07)

*publication bias based on the Egger Test

Estimated pooled adjusted odds ratio

The pooled adjusted odds ratio of opium on esophageal cancer was 1.68 (95% CI: 1.36, 2.08), for bladder cancer was 5.00(95% CI: 3.76, 6.66), for head and neck cancer was 4.93 (95% CI: 2.41, 10.06) for pancreatic cancer was 2.4 (95% CI: 1.62, 2.56) for lung cancer was 2.89(95% CI: 2.14, 3.30) for laryngeal cancer was 6.76 (95% CI: 3.77, 11.80) for gastric cancer was 3.13 (95% CI: 1.92, 5.11) and for colorectal cancer was 2.51 (95% CI: 1.04, 6.07).All association were statistically significant (Fig. 3).

Discussion

This systematic review aims to examine the relationship between opium use and various types of cancer. A comprehensive search yielded a total of 1,907 articles, of which 32 case-control and six cohort studies met the eligibility criteria for inclusion in the final analysis. The combined sample size across these studies consisted of 523,827 participants, revealing moderate heterogeneity in the results. The innovation of this review study was the incorporation of a greater number of studies, as well as the application of adjusted effect sizes and the exclusion of crude effect sizes.

The review encompassed a significant portion of studies (90%) conducted in Golestan province, situated in northeastern Iran. This concentration of research in the region is unsurprising, as Golestan is part of the esophageal cancer belt and has the highest prevalence rate of esophageal cancer in the world. Importantly, rigorous studies have been conducted in Golestan province to evaluate the risk factors linked to this disease. In other hand, given the high prevalence of opium consumption in Iran due to its neighboring country of Afghanistan, it is unsurprising that the majority of studies in the field of opium and cancer are conducted in this region.

Table 3 Association of opium and cancer-GRADE evidence profile

Cancer Type	No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	OR (95%CI)	Certainty
Bladder	13	Serious[a]	Serious[b]	Not Serious	Not Serious	Serious[c]	5.00 (3.76, 6.66)	Very Low
Esophageal	6	Serious[a]	Not Serious	Not Serious	Not Serious	Serious[c]	1.68 (1.36, 2.08)	Very Low
Pancreatic	5	Serious[a]	Not Serious	Not Serious	Not Serious	Serious[c]	2.04 (1.62, 2.56)	Very Low
Lung	5	Serious[a]	Not Serious	Not Serious	Not Serious	Not Serious	2.89 (2.14, 3.90)	Moderate
Laryngeal	4	Serious[a]	Serious[b]	Not Serious	Not Serious	Not Serious	6.67 (3.77, 11.80)	Very Low
Gastric	5	Not Serious	Serious[b]	Not Serious	Not Serious	Not Serious	3.13 (1.92, 5.11)	Moderate
Colorectal	3	Not Serious	Serious[b]	Not Serious	Not Serious	Not Serious	2.51(1.04, 6.07)	Moderate

a: Risk of bias were rated low or moderate using the Newcastle-Ottawa Scale (i.e., score < 8). for Balder Cancer: 25.0% studies were weak quality, for Esophageal cancer: 50% studies were weak and moderate, for Pancreatic and lung cancers 40% studies were weak and moderate, for Laryngeal cancer: 60% studies were weak and moderate, b: heterogeneity (I^2) in case-control studies was 83.12%, d: b: Considerable Heterogeneity was observed based on I^2 ($I^2 \geq 50\%$). C: publication bias (based on the Egger test, $p < 0.05$) was observed

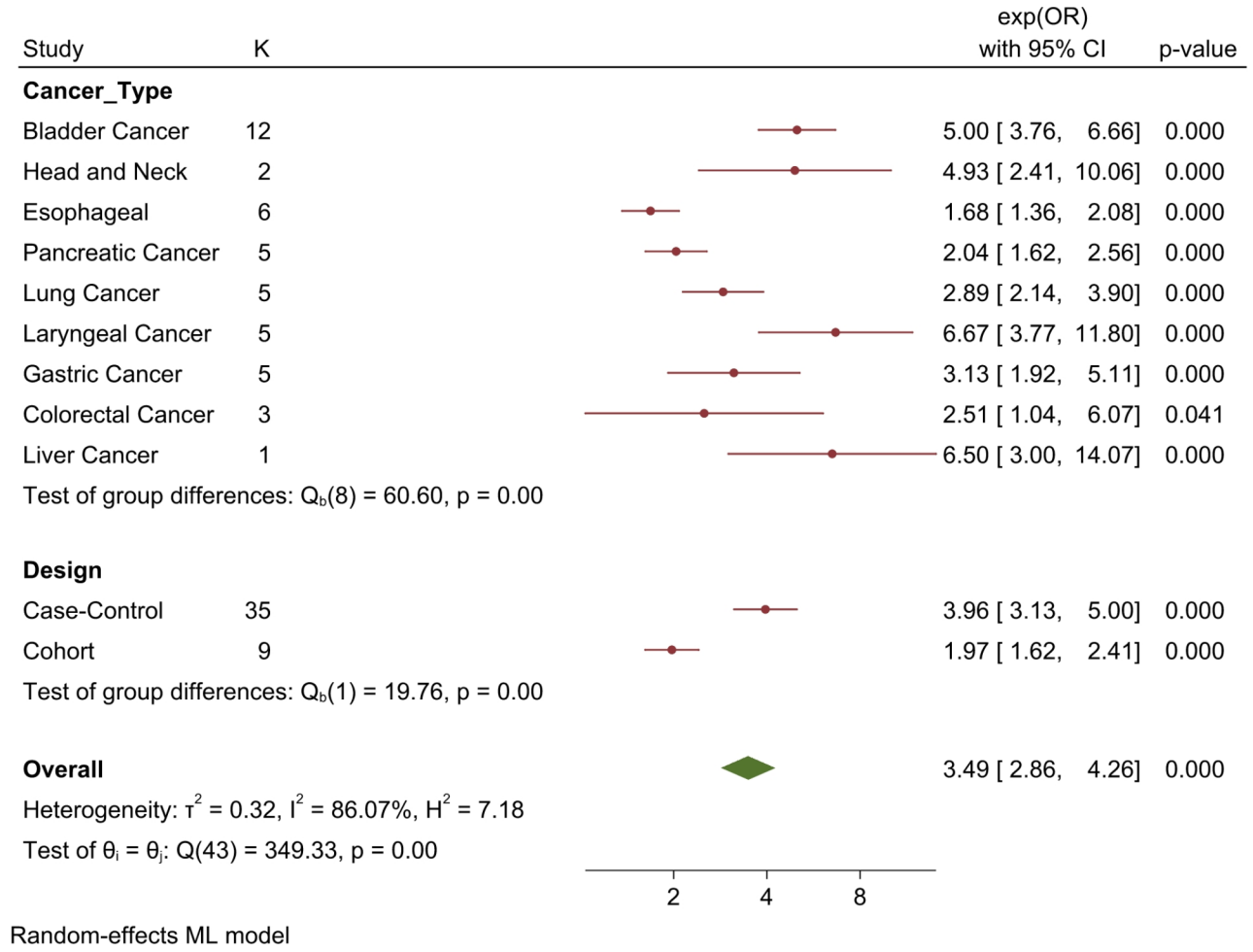

Fig. 3 The Pooled Adjusted Odds Ratio of opium on cancers

The meta-analysis indicated that all calculated odds ratios were greater than 1, the 95% CI suggesting statistically significant associations between opium use and an increased risk of developing several cancers. Among these, laryngeal cancer exhibited the highest odds ratio (6.67), illustrating a particularly strong link to opium usage. These findings highlight the significant health risks associated with opium consumption, indicating an urgent need for public health interventions and further scientific inquiry.

A significant concern pertains to the deleterious by-products generated during opium combustion, including polycyclic aromatic hydrocarbons (PAHs) and nitrosamines, both of which are acknowledged as carcinogens. These compounds have the potential to inflict damage to DNA, induce oxidative stress, and disrupt cellular

signaling, thereby contributing to the initiation and progression of cancer [50]. Furthermore, chronic exposure to opium smoke has been demonstrated to weaken the immune system's capacity to discern and eradicate cancerous cells, thereby facilitating tumor development [51, 52].

Opium usage is associated with various health risks, especially its potential links to lung and laryngeal cancer [53]. Chemicals in opium, including certain carcinogens and toxic substances released during its combustion, can lead to cellular mutations and increase cancer risk. Moreover, many opium users also engage in tobacco smoking, a confirmed major risk factor for laryngeal cancer, thus exacerbating the cancer risk [54]. Epidemiological data suggest elevated rates of head and neck cancers, such as laryngeal cancer, in regions with prevalent opium use, indicating a possible correlation influenced by environmental and lifestyle factors [55]. The multifactorial nature of laryngeal cancer development, encompassing both genetic and lifestyle influences, necessitates additional research to delineate the specific impact of opium use [56]. While there appears to be an association, especially with concurrent tobacco use, more extensive studies are essential to establish a direct causal relationship. Mitigating or eliminating both opium and tobacco use could significantly reduce laryngeal cancer risk and improve overall health outcomes.

About the role of opium on bladder cancer: previous research, particularly from Iran and Afghanistan, suggests that chronic opium use may correlate with an elevated risk of bladder cancer, attributed to carcinogenic compounds present in opium and its impurities [16]. Furthermore, opium users might face heightened exposure to environmental carcinogens associated with bladder cancer [49]. Although the precise mechanisms remain under investigation, the link between opium consumption and bladder cancer underscores the necessity for continued research to evaluate the implications of opium use on urinary tract health and cancer risk [57].

Opium Use and Gastrointestinal and esophageal Cancers: A notable meta-analysis has identified a significant association between opioid use and an increased risk of esophageal and gastric cancers, with an adjusted odds ratio indicating a 1.8-fold increase in risk [58]. This analysis predominantly encompassed studies from Golestan province, Iran, an area recognized for its high incidence of esophageal cancer. A significant prospective cohort study conducted over a decade (2007–2017) in Golestan, which included 68,024 residents, reported substantial age-specific incidence rates of esophageal cancer, particularly squamous cell carcinoma (SCC) [59]. Contributing factors associated with heightened risk included the consumption of very hot tea, fried meat, a family history of the disease, Helicobacter pylori infection, tobacco use, and crucially, opium consumption.

Opium Use and pancreatic Cancers: Opioids play a complex role in the management of pain associated with pancreatic cancer, one of the most painful and aggressive malignancies. Because patients often experience severe abdominal pain, opioids are often prescribed as part of palliative care to improve quality of life. However, the use of opioids is not without challenges, including concerns about addiction, side effects and potential interactions with other treatments [60]. In addition, there is growing interest in understanding their impact on cancer biology, as some studies suggest that opioids may influence tumor growth and metastasis through various mechanisms, including immune modulation [4]. Therefore, while opioids are essential for pain management in patients with pancreatic cancer, their broader implications warrant careful consideration in treatment plans, balancing pain relief with potential risks., so finally this association may be related to "reverse causation".

Palliative care is essential in alleviating pain and enhancing the quality of life for patients with advanced cancer. This approach utilizes a range of analgesic methods, such as opioids, non-opioid medications, and adjunct therapies. Recent studies have raised concerns regarding a possible association between analgesic use, particularly opioids, and the risk of carcinogenesis. Specifically, there is a suggestion that long-term opioid administration might affect tumor progression or metastasis [61, 62]. Nevertheless, the existing evidence remains ambiguous, underscoring the importance of a balanced strategy that emphasizes effective pain management while also weighing potential risks.

In the future, an integrated model that combines multimodal analgesia with careful monitoring of cancer progression, along with continued investigation into the biological impacts of analgesics on tumors, has the potential to improve patient outcomes and address safety issues within palliative care environments.

Strengths and limitations of the study should be considered. Two of the study's objectives was to estimate the relative risk of opioid use in relation to esophageal cancer occurrence and the majority obtained results were based on odds ratios, which tend to yield larger estimates than relative risks. Despite these limitations, this study was the first of its kind, and its results, which statistically strengthen the role of opium use as a risk factor, can inform planning efforts aimed at addressing underlying risk factors for cancers. The findings underscore the potential carcinogenic effects of opium, necessitating further research and public health interventions to address opium use and its associated health risks. Also, variation in opiate type, duration of use, or co-exposure to tobacco would strengthen the analysis. Subgroup analyses

focusing on these factors might provide more targeted insights, so we suggest that future studies improve their reporting based on more subgroups. Finally, since all the studies included in this review were conducted in Iran, the overall findings may not be broadly applicable due to the range of risk factors associated with cancer. Cancer is a multifaceted disease influenced by cultural backgrounds, socio-economics status, biological predispositions, race, and ethnicity. Therefore, it is essential to conduct rigorous, evidence-based studies across diverse communities to better understand the role of opioid drugs in cancer incidence. Such research is vital for clarifying the relationship between opioid use and cancer risk in various populations.

The comprehensive review by Li and others shows that lower SES is consistently associated with higher incidence of various cancers, poorer survival, and reduced access to timely and effective treatment. The review emphasizes the importance of addressing socioeconomic inequalities in cancer prevention and care to improve health outcomes in diverse populations [63]. However, due to the lack of reporting of cancer incidence by socioeconomic factors in the included studies, we were unable to subgroup cancer incidence by socioeconomic rank, and only 28% of the included studies in this review controlled for socioeconomic factors when estimating the effect of opiates on cancer.

Conclusions

Overall, this systematic review highlights a significant association between opium use and an increased risk of developing various cancers, notably laryngeal, bladder and head and neck. While a correlation exists, further comprehensive studies are needed to elucidate the causal mechanisms and to inform public health strategies aimed at reducing opium consumption and its associated health risks.

Also, the high prevalence of opium uses in regions such as Iran poses significant public health challenges, necessitating comprehensive policy responses. Strategic initiatives must encompass the augmentation of access to addiction treatment services, the implementation of educational campaigns that elucidate the perils associated with opium use, and the cultivation of alternative livelihood opportunities for individuals engaged in opium trafficking. In light of the established correlation between opium use and an elevated cancer risk, the implementation of targeted screening programs for high-risk populations is imperative. These programs should prioritize early detection and be tailored to align with the specific needs of the respective communities. Addressing the underlying causes of opium dependence and enhancing healthcare systems are pivotal for developing a sustainable, health-focused approach to this critical issue.

Abbreviations

ICD	International Classification of Diseases
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Author contributions

Conceptualization: BA, Data processing: BA. Methodology: BA, NA. Formal analysis: ZCh. Writing original draft: BA. Writing review & editing: BA, ZCh, NA.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

this study was approved (IR.UMSHA.REC.1402.249) in on Ethics Board of the Hamadan university of Medical Science.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to declare for this study.

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