Addiction & Health

https://ahj.kmu.ac.ir
10.34172/ahj.1533
AHJ. 2025;17:1533

Review Article

The Effect of Opioid Use on Esophageal Cancer: A Systematic Review and Meta-analysis

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Abstract

Background: There is limited research available on the direct effect of opioid use on esophageal cancer. The objective of this systematic review and meta-analysis is to consolidate the results of previous studies and provide an estimate of the pooled relative risk or odds ratio associated with opioid use in relation to the occurrence of esophageal cancer.

Methods: The PRISMA guidelines were utilized to establish a framework for conducting this systematic review and meta-analysis. A systematic search was conducted in international and national databases. PubMed, Web of Science, Scopus, and national electronic databases were searched up to February, 2024. The random-effects model was used to report the results at a 95% confidence interval (CI). Stata 11 was used for data analysis.

Findings: Out of the 648 retrieved articles, 11 studies remained in the final analysis (one cohort study and ten case-control studies). In all subgroups analyzed based on the type of odds ratios, no significant heterogeneity was observed. The pooled adjusted odds ratio of opium on esophageal cancer was 1.8 (95% CI: 1.24–2.61), and the pooled crude odds ratio of opium on esophageal was 1.82 (95% CI: 1.55–2.14).

Conclusion: The results of this systematic review and meta-analysis showed that there is a significant relationship between opium use and esophageal cancer, and opium can be a serious risk factor for esophageal cancer.

Keywords: Opium, Esophageal cancer, Systematic review, Meta-analysis

Citation: Cheraghi Z, Azmi-Naei N, Ameri M, Azmi-Naei B. The effect of opioid use on esophageal cancer: a systematic review and meta-analysis. *Addict Health*. 2025;17:1533. doi:10.34172/ahj.1533

Received: February 4, 2024, **Revised:** March 18, 2024, **Accepted:** March 8, 2025, **ePublished:** March 10, 2025

Introduction

Cancer is a significant cause of death globally, and its prevalence and incidence are steadily rising. In 2020, esophageal cancer was ranked as the eighth most common cancer worldwide and stood as the sixth leading cause of cancer-related deaths, resulting in approximately 544,076 fatalities annually.[1] The five-year survival rate for this type of cancer ranges between 15% and 25%.[2]. Esophageal cancer is categorized into two primary cell groups: squamous cell carcinoma (SCC) and adenocarcinoma, both of which exhibit a five-year survival rate of less than 10%. In Iran alone, it is estimated that out of 35 000 cancer-related deaths, approximately 5,800 are attributed to esophageal cancer. It is the second leading cause of cancer mortality in the Middle East according to the World Health Organization (WHO).[3] The incidence of squamous cell esophageal cancer is particularly high in Iran, Turkey, Kazakhstan, and northern China, with an incidence rate surpassing 100 cases per 100 000 population annually.[4]

The incidence rate of esophageal cancer exhibits variations across different regions worldwide,[5,6] including within different provinces of Iran, where it can differ by up to a factor of 20 depending on the region.[7] Numerous risk factors have been associated with the development of esophageal cancer. In recent studies, particular attention has been given to the role of diet in relation to this disease, examining various aspects of dietary behavior. In Iran, low consumption of vegetables and fresh foods has been identified as a contributing factor for esophageal cancer.[8,9] For instance, in northern Iran, high consumption of wheat, drug use, and hot tea drinking have been identified as risk factors for esophageal cancer. Additionally, tobacco use, alcohol consumption, and elevated levels of nitrates in water have been reported as environmental factors influencing the occurrence of esophageal cancer.[10-13]

Another factor that is believed to contribute to the onset of esophageal cancer is opium use.[14] The prevalence of opium addiction in Iran has tripled over the past 20 years, reaching 8.2%. The overall prevalence of drug-related illnesses recorded in primary care centers is between 7% and 8%.[15,16] Opium has been associated with an increased risk of several types of cancer, including esophageal,[17] pancreatic,[18] stomach,[19,20] bladder,[21] lung,[22,23] and laryngeal[24,25] cancers.

The International Agency for Research on Cancer (IARC) has classified opium as a Group I carcinogen, and it has been identified as a contributing factor for the development of esophageal cancer.[26]

Global reports on drug use indicate a concerning upward trend in opium consumption worldwide, resulting in a growing burden of drug-related illnesses on a global scale.[26-29] It is estimated that approximately 16.5 million individuals are illicit opium users. Interestingly, studies have revealed that opium can exhibit cancer-suppressing properties through various mechanisms.[30] This finding raises concerns, particularly in studies where opioids are commonly used for pain management, including cancer-related pain.[31]

While some studies have established a correlation between opium use and the risk of esophageal cancer, others have not found a significant association.[17,32,33] Given the significance of esophageal cancer and the increasing use of opioids, a meta-analysis was deemed necessary to consolidate the findings of previous studies and estimate the relative risk associated with opioid use in relation to the occurrence of esophageal cancer.[34] Therefore, the objective of this study was to summarize the results of prior research and provide an estimation of the odds ratio associated with opioid use in relation to the occurrence of esophageal cancer.

Methods

This review has been conducted in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines.

Search strategy

A search was conducted on international databases, including PubMed, Web of Science, Scopus, and Google Scholar, up to February 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 including "esophageal cancer/s," OR "esophageal malignancy/ies," OR "esophageal neoplasm/s," OR "esophageal tumor/s," AND " opioid" OR "opium."

Eligibility criteria

In this systematic review, we included analytical observational studies encompassing cross-sectional, case-control, and cohort designs that investigated the association between opium use and the risk of esophageal cancer. Studies that provided the necessary data to report effect sizes in the form of relative risk or odds ratio were included. The primary outcome of this study is the occurrence of esophageal cancer, which had to be confirmed through pathological methods or medical diagnosis, and the classification of cancers had to be validated based on the International Classification of Diseases (ICD-10) criteria.

The study population considered in this review encompasses individuals at risk of developing various types of cancer across all age groups without restrictions based on country, age, gender, or ethnicity. The primary focus remains on esophageal cancer, and its diagnosis and classification must adhere to the ICD-10 criteria. Furthermore, there were no restrictions on the publication dates of the studies, geographical locations, or languages in this review, ensuring a comprehensive inclusion of relevant research.

Study selection

Following the search conducted in databases, the obtained results were imported into EndNote software, which facilitated the removal of duplicate records. Two investigators were assigned to independently and concurrently screen the titles and abstracts of the identified studies. In cases where there was any disagreement, a resolution was reached through discussion and the involvement of a third investigator. Additionally, the agreement between the two researchers was assessed using the kappa index, which yielded a value of 0.88, indicating substantial agreement.

The full texts of the selected studies were downloaded to gather more comprehensive information. Finally, based on the inclusion criteria, the studies that met the specified criteria were included in the review. A total of 907 articles were identified. Among these, 256 articles were duplicates, and 442 were excluded after their titles and abstracts were screened.

Data extraction

After thoroughly reviewing the full texts of the eligible studies, relevant information was extracted and recorded in a pre-designed datasheet. The extracted data included the following key elements: author's name, year of publication, study location (country), mean age of participants, gender distribution, total sample size, crude and adjusted odds ratios, upper and lower limits of odds ratios, adjusted factors included in the statistical models, and number of cases and controls in the exposed and non-exposed groups.

These collected data are intended for further analysis and examination of the results obtained from the included studies. By utilizing this information, relevant reports can

be prepared, offering a comprehensive understanding of the relationship between opium use and the risk of esophageal cancer.

Risk of bias assessment

The quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS). The specific items used for quality assessment in this review were as follows: (1) assessment of outcome, (2) ascertainment of exposure, (3) definition of controls, (4) selection of controls, and (5) reporting precision for the outcome (95% CI). This quality assessment scale determines the quality and level of bias in studies, assigning a maximum of nine stars. High-quality studies are those that have been awarded at least seven stars.

Heterogeneity and publication bias

Statistical heterogeneity was evaluated through the application of the chi-square test at the 10% significance level. Furthermore, the heterogeneity was quantified using the I^2 statistic. Between-study variance was estimated using the tau-square statistic (denoted as Ta^2). In order to address the issue of heterogeneity, we employed two distinct approaches. The first of these entailed a thorough reexamination of the extracted data. The second approach was as follows: a random-effects model was employed. In addition, we used the funnel plot to examine the publication bias visually and Egger's tests at the significance level of 0.05 to ascertain publication bias statistically.

Data synthesis

We calculated the odds ratios (ORs) in each study by dividing the multiplication of the cases exposed (a) and the controls unexposed (b) by the multiplication of the cases unexposed (c) and the controls exposed (d) using the following formula:

$$\mathrm{OR} = \frac{a \times d}{b \times c} \tag{1}$$

In addition, the standard error odds ratios in the logarithmic scale were calculated as follows:

$$\text{Standard Error of Ln}\left(\mathrm{OR}\right) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}} \tag{2}$$

For studies that had not reported the number of cases and controls by exposure level, we calculated the standard error in a logarithmic scale with a 95% confidence interval using the following alternative formula:

$$\text{Standard Error of Ln}\left(\mathrm{OR}\right) = \frac{\text{Upper limit of OR} - \text{Lower limit of OR}}{2 \times 1.96} \tag{3}$$

In order to obtain the odds ratios, the inverse variance method was employed. The random effects model was used to report the results at 95% CI. Finally, Stata 11 (Stata Corp, College Station, TX, USA) was used for data analysis at a 95% confidence interval.

Results

After conducting a thorough search of databases, including PubMed, Scopus, and Web of Science, until February 11, a total of 907 articles were identified. Among these, 256 articles were duplicates, and 442 were excluded after their titles and abstracts were screened. Subsequently, a re-evaluation was performed on 209 articles, excluding 198 articles either due to not meeting the inclusion criteria or a lack of access to the full text. Finally, one cohort study and ten case-control studies were included in our analysis. The sample size in the ten case-control studies comprised 5389 individuals, and the cohort study encompassed 50,034 individuals (Figure 1). A comprehensive presentation of the characteristics of all included studies is provided in Table 1.

Synthesis of results

All the included studies have been conducted in Asian countries, including Iran. The analysis included one cohort study and ten case-control studies. Among the case-control studies, two studies were conducted by the same research team in a specific region, reporting two different odds ratios. Both studies used the same case definition but employed different control groups (hospital control and neighborhood control).

Heterogeneity and publication bias

The I^2 and chi-square tests were utilized to assess both quantitative and qualitative heterogeneity among the studies with a significance level of 0.05. The tau-squared test was also employed to estimate the studies' variances. In all subgroups analyzed based on the type of odds ratios, no significant heterogeneity was observed. Furthermore, Cochran's test ($P > 0.05$) indicated that these inconsistencies were not statistically significant.

When evaluating publication bias, the distribution of studies was examined visually. The studies were distributed in a nearly symmetrical manner on both sides of the vertical line, suggesting the absence of publication bias. Egger's tests were conducted for both the crude ($P = 0.896$) and adjusted odds ratios ($P = 0.575$) to further confirm the absence of publication bias. The results of these tests supported the conclusion that there was no publication bias in the studies (Figure 2).

Risk of bias assessment

In the current study, 63.6% of studies ($n = 7$) had good reporting quality, while 27% of studies ($n = 3$) had moderate quality, and 0.09% ($n = 1$) had low quality.

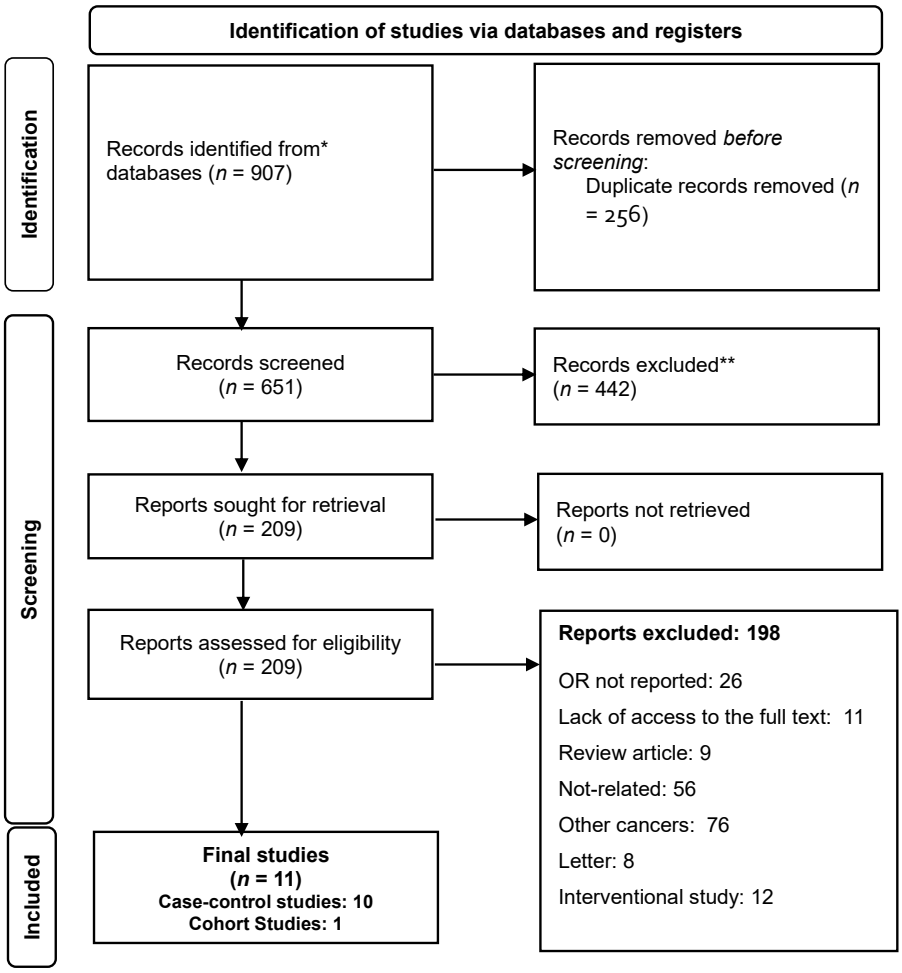

Figure 1. A flow diagram depicting the phases of retrieving articles, checking eligibility criteria, and including the articles in the meta-analysis

Table 1. The characteristics of included studies.

First author, Publication Year	City*	Mean of age	Study design	Gender	Crude OR	Adjusted OR	Sample size	Quality (risk of bias)
Sepehr, 2005[34]	Golestan	NR	Case-control	Both	0.93	0.89	174	Good
Shakeri, 2012[35]	Gonabad	NR	Case-control	Both	1.37	1.09	390	Good
Pournaghi, 2019[36]	North Khorasan	NR	Case-control	Both	NR	2.1	283	Weak
Nasrollahzadeh (a), 2008[17]	Golestan	64.4	Case-control	Both	2.22	2.12	871	Moderate
Etemadi, 2012[37]	Golestan	64.4	Case-control	Both	1.8	NR	871	Good
Hakami, 2014[38]	Golestan	62.5	Case-control	Both	3.79	10.11	120	Moderate
Nasrollahzadeh (c), 2015[39]	Golestan	64.4	Case-control	Both	1.83	NR	812	Good
Islami, 2009[32]	Golestan	NR	Case-control	Both	1.75	NR	871	Good
Bakhshaee, 2017[24]	Mashhad	NR	Case-control	Both	1.44	NR	180	Moderate
Nasrollahzadeh (b), 2012[40]	Golestan	65.1	Case-control	Both	1.63	NR	817	Good
Sheikh, 2020[41]	Golestan	52.05	Cohort	Both	1.08	1.038	50034	Good

* All studies were conducted in Iran. NR: Not reported.

The estimated pooled crude odds ratio

Based on the ten case-control studies that reported the crude odds ratio of opium on esophageal cancer, the overall crude odds ratio was calculated using a random-effects model. The results showed that the crude odds ratio of the effect of opium use on esophageal cancer was 1.82 (95% CI: 1.55–2.14). This suggests a significant association between opium consumption and the risk of esophageal cancer (Figure 3).

Estimated pooled adjusted odds ratio

Based on the eight case-control studies that reported

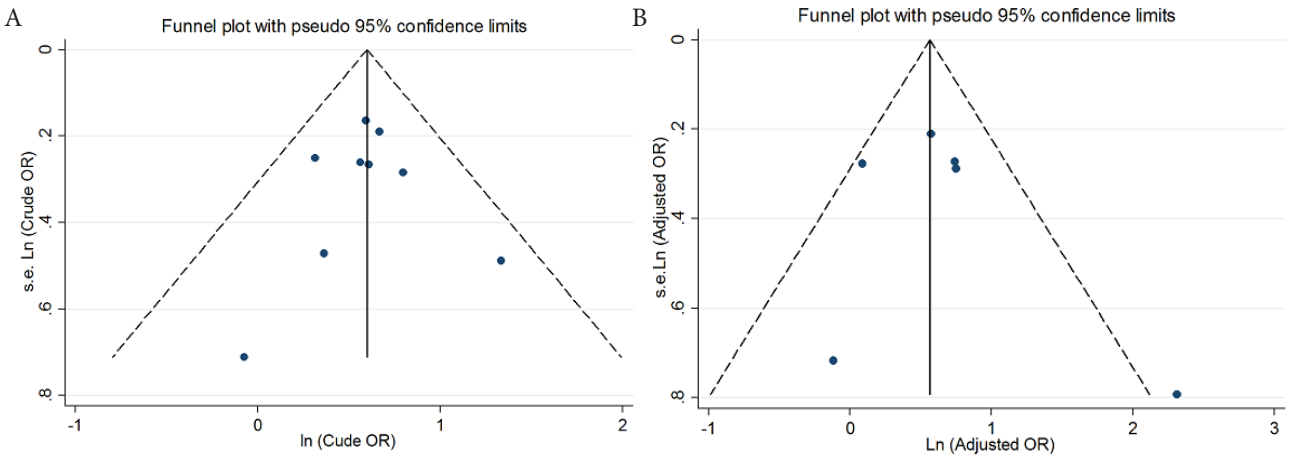

Figure 2. A: funnel plot of included studies (in crude odds ratio situation), B: funnel plot of included studies (in adjusted odds ratio situation)

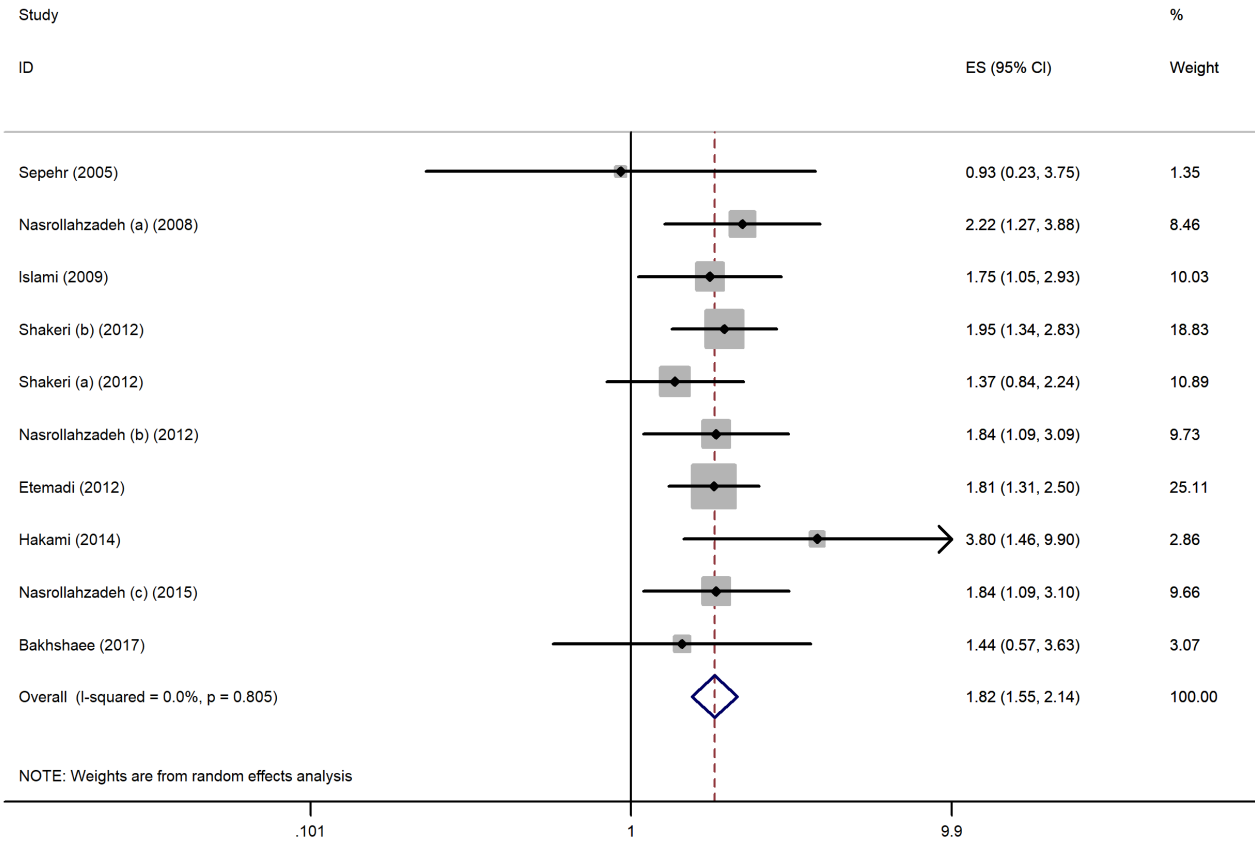

Figure 3. The pooled crude odds ratio of the effects of opium use on esophageal cancer

the adjusted odds ratio of the effect of opium use on esophageal cancer, the overall adjusted odds ratio was calculated using a random-effects model. The results showed that the adjusted odds ratio of the effect of opium use on esophageal cancer was 1.8 (95% CI: 1.24–2.61). This indicates a significant association between opium consumption and the risk of esophageal cancer, even after adjusting for potential confounding factors (Figure 4). The list of adjusted factors in each study is given in Table 1.

Discussion

In this systematic review, a comprehensive search yielded 648 articles. After thorough screening and selection, ten case-control studies were deemed eligible for inclusion in the final analysis. The collective sample size of these studies amounted to 5389 participants. The analysis

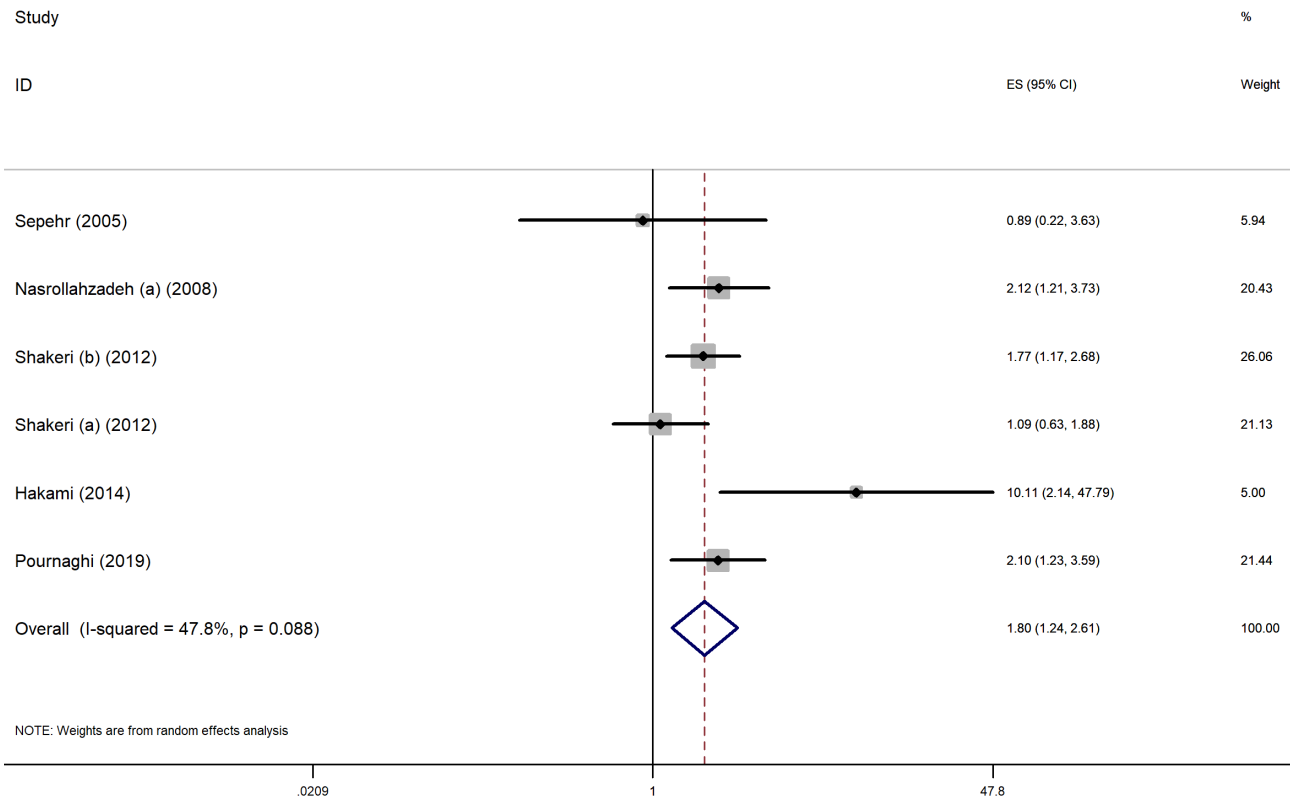

Figure 4. The pooled adjusted odds ratio of the effects of opium use on esophageal cancer

did not reveal significant heterogeneity in the results. This suggests that the findings across the studies were consistent and comparable, allowing a meaningful meta-analysis.

Furthermore, an assessment of publication bias indicated that the included studies did not exhibit biases in their reporting. However, it is important to note that the absence of publication bias could be influenced by the small sample size of the present study, which involved a limited number of included studies. It is important to interpret the results with caution, considering the potential impact of the study's sample size on the observed outcomes.

The findings of the meta-analysis revealed that there is a significant association between opioid use and the risk of developing esophageal cancer. When considering the crude odds ratio, the analysis showed that opioid use is associated with a 1.82-fold increase in the risk of esophageal cancer (95% CI: 1.55–2.14). Additionally, when adjusting for other factors, the adjusted odds ratio indicated a significant (1.8-fold) increase in the risk of esophageal cancer with opioid use (95% CI: 1.26–2.61). These results suggest that opioid use is a potential risk factor for the development of esophageal cancer, even after accounting for other confounding factors. The review included a substantial proportion of studies (90%) conducted in Golestan province, located in northeastern Iran. This high concentration of studies in the region is not surprising, given that Golestan province in Iran is located in the esophageal cancer belt and has one of the highest prevalence rates of esophageal cancer globally.[42,43] Therefore, valid studies have been carried out in Golestan province to assess the risk factors associated with esophageal cancer.[3,17,34,36]

One noteworthy study conducted in this region is a prospective cohort study that spanned 10 years from 2007 to 2017. The primary objective of this study was to identify the risk factors for various diseases, including esophageal cancer. The cohort study included 68 024 residents aged between 40 and 75 years in the eastern region of Golestan province. The findings of this extensive study revealed that the age-specific incidence rate of esophageal cancer, predominantly SCC, was 114.5 and 147.5 per 100 000 among women and men, respectively, in 2017.[44] The findings of these studies indicate that several factors are associated with an increased risk of esophageal cancer. These include drinking very hot tea (OR = 10), consumption of roasted and fried meat (OR = 8), having a family history of esophageal cancer (OR = 2.3), *Helicobacter pylori* infection (OR = 2), tobacco use (OR = 1.8), and notably, opium use (OR = 2.6).

In relation to the role of opioids in the incidence of esophageal cancer, the first study conducted in Iran was carried out by Ghadrian et al in Golestan province in 1985. The study's most significant finding was the association between the presence of morphine metabolites in urine, indicative of opioid use, and esophageal cancer.[45] Given the prevalence of opium consumption in Golestan

province, particularly among rural males (with some studies reporting opioid use prevalence rates of up to 33% in the region[34]), there is a compelling hypothesis that the drug is a risk factor for esophageal cancer.

Despite the common use of opioids for traditional treatments, including pain, diarrhea, and insomnia in Golestan province, there is evidence suggesting that specific derivatives obtained from opium, like sukhteh, may have mutagenic properties due to the presence of compounds such as polycyclic aromatic hydrocarbons (PAH).[33] Studies conducted in Golestan have indicated that the consumption of residual materials from opium (e.g., shireh and sukhteh) is more prevalent due to its lower cost compared to pure opium, further reinforcing the hypothesis.[45] Additionally, numerous studies have demonstrated the carcinogenic effects of opioid combinations, including opium, on various types of cancer such as lung cancer, gastric cancer, and bladder cancer.[17,46,47]

It is important to note that the specific type of opioid use (oral consumption or smoking through direct heating with burning charcoal) and the duration of opium consumption can potentially yield different results. Unfortunately, these details regarding substance abuse were not consistently reported in the studies, making it difficult to distinguish the effects of different opioid components on the occurrence of gastrointestinal cancers, including esophageal cancer.

Furthermore, a cohort study conducted by Malikzadeh et al[47] demonstrated that long-term opioid use increases the risk of death from esophageal cancer by 1.8 times when adjusted for other risk factors including age, sex, alcohol consumption, ethnicity, and viral hepatitis.

The strengths and limitations of the study should be considered. One of the study's objectives was to estimate the relative risk of opioid use in relation to esophageal cancer occurrence. However, no primary cohort study with this specific goal was identified in the search, and the obtained results were based on odds ratios, which tend to yield larger estimates than relative risks. Another limitation was that only five of the ten studies reported adjusted odds ratios, resulting in a meta-analysis based on only four studies. Additionally, some studies measured the effects of opioid drugs on all gastrointestinal cancers collectively, without evaluating them individually, leading to their exclusion from the meta-analysis. Therefore, it is recommended that future studies provide more detailed results to optimize their applicability. 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 chronic diseases, including esophageal cancer.

Conclusion

The systematic review conducted on this topic revealed a significant association between opium use and esophageal cancer. The findings strongly indicate that opioids can serve as a significant risk factor for the development of esophageal cancer.

Acknowledgments

The authors would like to thank the Vice-Chancellor of Research and Technology of Hamedan University for approving this study (Code: 140203302443).

Authors' Contribution

Conceptualization: Zahra Cheraghi and Bita Azmi-Naei.
Methodology: Bita Azmi-Naei, Nazanin Azmi-Naei, and Mohadase Ameri.
Visualization: Bita Azmi-Naei, Nazanin Azmi-Naei, and Mohadase Ameri.
Writing–review & editing: Bita Azmi-Naei, Nazanin Azmi-Naei, Zahra Cheraghi, and Mohadase Ameri.

Competing Interests

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

Ethical Approval

Hamedan University of Medical Sciences Ethics Board (IR.UMSHA.REC.1402.249) has approved this study.

Funding

No sources of support were provided.

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