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Review Article

Does Opium Consumption Have Shared Impact on Atherosclerotic Cardiovascular Disease and Cancer?

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Abstract

Although atherosclerotic cardiovascular disease (ASCVD) and cancer are seemingly different types of disease, they have multiple shared underlying mechanisms and lifestyle-related risk factors like smoking, unhealthy diet, excessive alcohol consumption, and inadequate physical activity. Opium abuse is prevalent in developing countries, especially the Middle East region and many Asian countries. Besides recreational purposes, many people use opium based on a traditional belief that opium consumption may confer protection against heart attack and improve the control of the risk factors of ASCVD such as diabetes mellitus, hypertension, and dyslipidemia. However, scientific reports indicate an increased risk of ASCVD and poor control of ASCVD risk factors among opium abusers compared with nonusers. Moreover, there is accumulating evidence that opium consumption exerts potential carcinogenic effects and increases the risk of developing various types of cancer. We conducted a review of the literature to review the current evidence on the relationship between opium consumption and ASCVD as well as various kinds of cancer. In addition, we will discuss the potential shared pathophysiologic mechanisms underlying the association between opium abuse and both ASCVD and cancer.

Keywords: Atherosclerosis, Cancer, Coronary artery disease, Opium, Tumor

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) and cancer are the two main causes of mortality and morbidity globally, accounting for two-thirds of all deaths in 2012.[1,2] The occurrence of ASCVD and cancer is rising in all socioeconomic classes throughout the world over due to population aging and changes in the distribution of major lifestyle-related risk factors. Although globally, there are 4 major shared risk factors for ASCVD and cancer (viz, unhealthy diet, sedentary lifestyle, chronic alcohol and tobacco consumption), there may be local or regional habits that may significantly contribute to the increasing burden of both ASCVD and cancer.[1,3-6] The importance of common adjustable risk factors for both ASCVD and cancer is redirected in our understanding of the mutual genetics and molecular mechanisms that are essential to the pathogenesis of both diseases.[7] Moreover, modifiable risk factors are promising targets for joint preventive efforts against ASCVD and cancer.[8]

The United Nations Office of Drugs and Crime (UNODC) estimates that in 2019, almost 30 million people consumed opium or its derivatives illegally around the globe.[9] Very recently, opium consumption was classified into Group I as carcinogenic by the International Agency for Research on Cancer (IARC).[10] While opium use and availability in developed countries have decreased over the years, opium is still the most regularly abused substance after tobacco, in developing countries such as the Middle East region, and many Asian countries.[11-13] In addition to availability, another reason for the high consumption of opium in these countries could be a traditional belief among Eastern people and even medical staff that opium consumption may have beneficial effects on health, particularly ASCVD as well as other cardiovascular risk

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factors including diabetes mellitus, hypertension, and dyslipidemia.[11,14-16] In the recent decade, numerous studies have been presented on humans and animals to evaluate the effect/association of opium consumption on/with various health outcomes.[17-21] Previously, we have reviewed the shared pathophysiologic pathways of ASCVD and cancer to show that these two are unexpectedly similar to each other.[8] In this narrative review, we will review the available evidence on the relationship between opium consumption and ASCVD as well as various kinds of cancer. Additionally, we will discuss the potential shared pathophysiologic mechanisms underlying the association between opium abuse and both ASCVD and cancer.

Association between Opium Consumption and ASCVD

There is a traditional belief among Asians that opium consumption may exert a beneficial effect on the cardiovascular system such as preventing heart attacks. During the past 15 years, many observational studies have been conducted to evaluate such beliefs, and they have found interesting results. We will separately review the studies on the association between opium consumption and each of stable coronary artery disease (CAD), acute coronary syndromes, and the outcomes of coronary revascularization.

Stable Coronary Artery Disease

Clinical Studies

The paucity of studies on mortality and morbidity among opium users has prompted scientists to conduct research on individuals with opium consumption and its relationship with ASCVD. A cross-sectional study by Sadeghian and colleagues on 2405 patients demonstrated that after adjustment for cardiac risk factors, opium consumption was significantly associated with the presence of CAD (odds ratio [OR] = 1.8, 95% confidence interval [CI] = 1.1 to 3.1; $P = 0.015$), and a dose-response relationship was observed between the dosage of opium consumption and the severity of CAD.[22] In another cross-sectional study, which investigated the predictors of premature CAD in the Iranian population, Sadeghian and colleagues found that high prevalence of opium consumption was the most important risk factor for premature CAD in male patients (OR = 4.47, 95% CI = 1.49 to 13.38; $P < 0.01$).[23] In another cross-sectional study, Hosseini et al evaluated 2874 opium consumers compared with 2568 non-consumers and found that opium use was an independent risk factor for CAD (OR = 1.31, 95% CI = 1.01 to 1.69; $P = 0.042$).[24] Darabad and colleagues conducted a survey on 1170 patients, including 121 opium-using patients, who underwent coronary angiography. They showed that opium addiction was associated with angiographically confirmed CAD. Nonetheless, they did not find any significant association between opium use and the number of affected coronary vessels.[25]

In addition to atherosclerotic disease of the major epicardial coronary arteries, it has been shown that opium use is related with microvascular coronary dysfunction (MCD). In a cross-sectional study on 250 Iranian patients with confirmed ischemic heart disease by exercise test and coronary angiography, Nadimi et al observed that opium addiction was the only factor associated with MCD (OR = 3.57, 95% CI = 1.42 to 9.02, $P = 0.0069$).[26]

There are other several studies on the association between opium consumption and CAD occurrence that have shown an increased risk of CAD in association with opium use.[27-30] One exception is an investigation by Rezvani et al who showed no significant association between opium consumption and ischemic heart disease.[31]

A summary of studies on the association between opium consumption and stable CAD and its outcomes is presented in Table 1.

Acute Coronary Syndromes

Despite consistency in the findings of studies evaluating the association between opium consumption and stable CAD, there is controversy among investigations regarding the possible association between opium consumption and the occurrence of acute MI and its short- and medium-term outcomes such as prolonged hospitalization, atrial fibrillation, and heart failure.[32] In a cross-sectional research, which was followed by a 1-year longitudinal cohort study on 690 patients with acute myocardial infarction (AMI), Roohafza and colleagues investigated the prevalence of opium dependency and the occurrence of short- and long-term events following AMI. They found that out of the 690 patients, 118 were opium-dependent. Opium dependency decreased age by 3.6 years (95% CI = 1.2 to 6.0; $P = 0.003$) for the occurrence of post-MI mortality and morbidity independent of cigarette smoking.[33] Harati et al[34] observed that those with opium dependency had almost significantly higher in-hospital mortality (11.5% vs 5.9%; $P = 0.072$) and significantly higher rehospitalization rates than nonusers (38.5% vs 13.7%; $P < 0.001$). Currently, many physicians do not advise their patients to quit opium consumption because of the fear of inducing a heart attack. Masoomi and colleagues conducted a remarkable study to evaluate whether opium withdrawal was a trigger for AMI. They evaluated 81 patients who had discontinued opium consumption and observed that after adjustments for demographic characteristics, marital status, education level, and common CAD risk profiles, opium withdrawal was not a trigger for AMI (OR = 0.920, 95% CI = 0.34 to 2.42; $P = 0.866$).[35] Dehghani et al also demonstrated that in-hospital mortality was not significantly different between 239 opium-addicted patients and 221 nonaddicted patients. Opium addiction was associated with lower occurrence of anterior wall MI (26.4% vs 36.4% in nonaddicted patients) and its related early mortality.[36] Recently, a systematic review and meta-analysis by Nakhaee et al evaluated the association between opium and CVD. They demonstrated a significant association between opium use and CAD but not in-hospital mortality (OR = 2.75, 95% CI = 2.04 to 3.75; $I^2 = 47\%$ vs OR = 1.44, 95% CI = 0.88 to 2.36; $I^2 = 51\%$).[32]

Table 1. Summary of Studies Evaluating the Association Between Opium Consumption and Stable Coronary Artery Disease and its Outcomes

Study Reference	Type of Study	Severity of Opium Consumption	Study Population	Results
Sadeghian et al, 2007 [22]	Cross-sectional	Use of opium ≥ 1 time in life	N = 2405 (322 opium users and 2083 nonusers)	A higher presence of CAD was observed in opium users than in nonusers (OR = 1.8, 95% CI = 1.1 to 3.1; *P* = 0.015). A significant dose-response relationship was detected between the dose of opium consumption and the severity of CAD based on the clinical vessel score (*r* = 0.2).
Masoomi et al, 2010 [28]	Cross-sectional	Addiction	N = 299 (118 opium addicts and 181 nonusers)	After adjustments for potential confounders, patients who frequently consumed opium were more expected to have severe CAD (OR = 1.82, 95% CI = 0.93 to 3.58; *P* = 0.08).
Masoomi et al, 2010 [27]	Nested case-control	Addiction	N = 91 (58 patients with CAD and 33 cases of normal coronary arteries)	Opium addiction was an independent risk factor for CAD in non-cigarette smoking cases (OR = 38; 95% CI = 2.7 to 531.7). However, in cigarette smokers, opium was not a significant risk factor (OR = 13.2; 95% CI = 0.85 to 206.5).
Sadeghian et al, 2010 [23]	Cross-sectional	Opium use	N = 940 (387 men aged < 45 y)	Opium usage was the most important risk factor for CAD in male patients younger than 45 years in Iranian sample (OR = 4.47, 95% CI: 1.49 to 13.38; *P* < 0.01).
Hosseini et al, 2011*[29]	Cross-sectional	Use of opium for ≥ 3 mon*	N = 456 (228 opium-using diabetic patients and 228 non-opium-using diabetic patients)	Higher severity and extension of coronary atherosclerosis were reported among opium-using diabetics than among age, sex, and smoking-matched non-opium-using diabetics. A significant independent dose-response relationship was observed between the dose of opium and the severity of opium consumption (β = 0.27; *P* = 0.04).
Rezvani et al, 2011 [31]	Cross-sectional	Addiction	N = 558 (161 opium addicts and 397 nonusers)	No association was found between opium consumption and ischemic heart disease.
Hosseini, 2012 [24]	Cross-sectional	Opium consumer	N = 5442 (2874 opium users and 2568 nonusers)	Opium was an independent risk factor for CAD (OR = 1.31, 95% CI = 1.01 to 1.69; *P* = 0.042).
Khademi et al, 2012 [30]	Cohort	Use of opium at least once a week for ≥ 6 mon	N = 50045 (8487 opium users and 41558 nonusers)	Increased risks of all-cause mortality were reported in opium users (adjusted HR = 1.86; 95% CI = 1.68 to 2.06). Increased risks of death from ischemic heart disease were reported in opium users (adjusted HR = 1.9, 95% CI = 1.57 to 2.29).
Darabad et al, 2014 [25]	Cross-sectional	Addiction	N = 1170 (121 opium-dependent cases and 1049 nonusers)	Opium dependence was independently associated with the presence of CAD (OR = 2.08; *P* = 0.019).
Nadimi et al, 2016 [26]	Cross-sectional	Addiction	N = 250 (125 patients with MCD and 125 individuals for comparison)	Opium addiction was an independent predictor of MCD (OR = 3.575, 95% CI = 1.42 to 9.02; *P* = 0.0069).

MI, myocardial infarction; OR, odds ratio; CAD, coronary artery disease; CABG, coronary artery bypass grafting surgery; CI, confidence interval; HR, hazard ratio; MCD, microvascular coronary dysfunction.
*97.3% of opium users (222 out of 228) were using opium for ≥ 12 months (unpublished data).

There are a few studies that have indicated no association between opium consumption and the increased incidence of MI[37] or in-hospital mortality.[14,38-40] Still, vis-à-vis the effects of opium on the cardiovascular system, there is always the presence of such intervening factors as the dose of drugs and the length and frequency of opium use, which should be considered. Additionally, research should take into account different routes of drug administration (e.g. inhalation, oral use, and injection), for which opium absorption and blood levels are different.[30]

The association between opium consumption and acute coronary syndromes and the related outcomes is demonstrated in Table 2.

Revascularization Studies

Based on traditional beliefs among people as well as some physicians, patients tend to continue opium consumption after coronary artery bypass grafting (CABG) surgery to improve the outcome of the operation. A cohort study on 566 isolated CABG patients was performed by Najafi and colleagues, who reported that opium consumption conferred no cardioprotective effects on addicted patients who underwent the operation. Nevertheless, they could not ignore the concurrent impact of cigarette smoking as a confounding variable.[42] Najafi et al also carried out a study on 268 patients with a confirmed diagnosis of CAD who had undergone isolated CABG. Of the 268 patients, only 38 were addicted at the time of the surgery. However, the authors found no significant vessel involvement in any of the groups, but the mean EuroSCORE was higher in the opium addicts than that in the nonaddicts.[43] Given the controversy surrounding the post-intervention continuation of opium consumption, in a retrospective study on 1545 patients with percutaneous coronary interventions history, Sharafi and colleagues evaluated the association between preprocedural opium consumption and major cardio-cerebrovascular events (MACCE). They found no significant correlation with MACCE between opium users and nonusers after percutaneous coronary interventions (11 [3.1%] vs 53 [4.4%]; P = 0.286, respectively). The unadjusted hazard of 1 year's MACCE in the opium users and nonusers was 0.704 (95% CI = 0.367 to 1.347; *P* = 0.289).[44]

Table 2. Summary of Studies Evaluating the Association between Opium Consumption and Acute Coronary Syndromes and their Outcomes

Study Reference	Type of Study	Severity of Opium Consumption	Study Population	Results
Azimzade-Sarwar et al, 2005 [37]	Case-control	Addiction	N = 300 (150 cases with acute MI and 150 controls)	No statistically significant association was found between opium addiction and acute MI.
Davoodi et al, 2005 [38]	Cohort	Addiction	N = 160 acute MI patients (45 opium-dependent patients and 115 non-opium-dependent cases)	Prolonged hospital stays were reported in opium addicts than in nonusers. Similar rates of in-hospital mortality and MACCE were reported during a 6-month follow-up.
Sadr-Bafghi et al, 2005 [14]	Nested case-control	Consumption of opium for > 12 mon	N = 556 acute MI patients (106 opium-users and 450 nonusers)	No significant difference was detected in in-hospital mortality (OR = 2.2, 95% CI = 0.9 to 5.1; $P = 0.057$).
Masoomi et al, 2011 [35]	Cross-sectional	Addiction	N = 81 opium-addicted patients	Opium withdrawal after adjustments for demographic characteristics, marital status, education level, and common CAD risk profiles was not a trigger for AMI (OR = 0.920, 95% CI = 0.340 to 2.419; $P = 0.866$).
Mirzaiepour et al, 2012 [40]	Cross-sectional	Addiction	N = 200 (94 opium addicts and 106 nonaddicts)	A higher frequency of post-MI arrhythmia was reported in opium-addicted subjects than in nonusers (80.9% vs 22.6%, respectively; $P < 0.001$). Opium addiction was an independent prognostic factor for the occurrence of post-MI arrhythmia (adjusted OR = 21.9; $P < 0.001$).
Roohafza et al, 2013 [33]	Cross-sectional Cohort*	Addiction	N = 690 (118 opium-dependent cases and 572 nonusers) N = 252 post-acute MI patients (126 opium-dependent cases and 126 age and smoking-matched nonusers)	Opium dependence independently caused a 3.6-year decrease (95% CI = 1.2 to 6.0; $P = 0.003$) in the age of acute MI/sudden cardiac deaths occurrence. Opium dependents and nonusers had similar rates of post-acute MI events, and mortality rates during a 12-month follow-up.
Khosoosi Niaki et al, 2013 [41]	Case-control	Consumption of opium for ≥ 12 mon	N = 236 (118 cases of acute MI and 118 controls)	Opium consumption was an important risk factor for acute MI (adjusted OR = 26.3, 95% CI = 7.5 to 92.4; $P < 0.0001$).
Dehghani et al, 2013 [36]	Cross-sectional	Addiction	N = 460 (239 opium-addicts and 221 nonaddicts)	The total in-hospital mortality rate was not notably different between the opium-addicted and nonaddicted groups. Opium addiction was associated with a lower occurrence rate of anterior wall MI (26.4% vs 36.4% in nonaddicted patients) and its early mortality.
Javadi et al, 2014 [39]	Cross-sectional	Addiction	N = 304 (152 opium-dependent cases and 152 nonusers)	Opium dependents and nonusers had similar rates of outcomes such as post-acute MI arrhythmia, prolonged hospital stay, and in-hospital mortality.
Harati et al, 2015 [34]	Retrospective cohort	Addiction	N = 400 (78 opium-dependent cases and 322 nonusers)	Opium dependents had a significant higher in-hospital death rate (11.5% vs 5.9%; $P = 0.072$) and a significantly higher rehospitalization than nonusers (38.5% vs 13.7%; $P < 0.001$).
Nakhaee et al, 2020 [32]	Systematic review, meta-analysis	Opium use	41 studies	Opium might be associated with CVD but not in-hospital mortality (OR = 2.75, 95% CI = 2.04 to 3.75; $I^2 = 47\%$ vs OR = 1.44, 95% CI = 0.88 to 2.36, $I^2 = 51\%$).

MI, myocardial infarction; OR, odds ratio; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio.
*An opium-dependent group and an age- and smoking-matched non-dependent group of living post-MI patients were followed up for 12 months.

Stroke

Hamzei-Moghadam et al conducted a cross-sectional study on 97 patients with ischemic stroke (38 addicts). They observed that one-third of the patients with ischemic stroke were addicted to opium and that the rate was higher than that in the general population.[45] In another case-control study, 672 patients with ischemic stroke were compared with 293 controls with no stroke or CAD history. In that study, Ebrahimi and colleagues found that opium addiction was independently associated with ischemic stroke (OR = 2.36, 95% CI = 1.16 to 4.85; $P = 0.018$).[46] More studies on the association between opium consumption and stroke are needed to clarify this relationship.

Peripheral Arterial Disease

Most studies indicate an association between ASCVD and opium consumption. There are limited studies evaluating the effects of opium on peripheral vascular disease. In a study by Shirani and colleagues, opium was assessed as a risk factor for significant carotid stenosis (≥ 70% the luminal diameter) in 939 patients with CABG. Although the authors did not detect any difference in the prevalence of significant carotid artery stenosis in opium-addicted versus nonaddicted patients, it should be noted that the opium-addicted patients had lower prevalence rates of hypertension (88.6% vs 11.4%) and diabetes (17% vs 11.4%) and a higher prevalence rate of smoking (27.1% vs 65.5%) than the nonaddicts.[47] However, Shirani et al did not adjust for confounding variables, and their findings should be interpreted cautiously. In another study, Jafarian et al[48] evaluated factors affecting graft patency in 85 patients who had undergone infrainguinal revascularization. They demonstrated that the patency rate was significantly lower in patients with opium use (32%) than nonusers (67%) ($P = 0.030$). It seems that more well-designed studies should be performed in the future to elucidate the effects of opium on peripheral vascular disease.

Association between Opium Consumption and ASCVD in Cohort Studies

The best corroborating evidence for a potential hazardous role of opium use in ASCVD derived from the Golestan

Cohort Study.[49] The Golestan Cohort Study enrolled 50 045 individuals between 40 and 75 years of age from January 2004 to June 2008 from the Golestan province, located in northern Iran. After a follow-up median of 4.7 years, the adjusted hazard ratio (HR) was 1.86 (95% CI = 1.68 to 2.06) for all-cause mortality associated with the opium consumption. The study also revealed that opium consumers were at 90% increased risk of mortality from ischemic heart disease (adjusted HR = 1.90; 95% CI = 1.57 to 2.29). Moreover, after omitting the subjects who had started opium use after receiving a diagnosis of a major illness (e.g. ischemic heart disease, cerebrovascular events, diabetes mellitus, and hypertension), the researchers discovered a dose-response association between the duration of opium consumption and ASCVD as well as all-cause mortality.[30] In a very recent publication of the Golestan Cohort Study, Nalini et al investigated the effects of long-term opiate use (crude opium or *shireh* [a derivative of opium made by boiling and filtering the opium, which has higher concentrations of morphine]) on cardiovascular mortality. They observed a significantly increased risk of mortality in opium users by comparison with nonusers (adjusted HR = 1.63; 95% CI = 1.49 to 1.79).[50] We think that there is a strong correlation between opium use and ASCVD based on the Golestan Cohort Study.

Association between Opium Consumption and Cancer

A popular belief among laypeople and also some physicians is that the use of opium can improve the survival of patients with malignancy. This belief might be due to the analgesic properties of opium that relieves pain in these patients. During the past few years, many studies have demonstrated a positive connection between opium consumption and the development of various types of cancers. More recent studies have explored the effects of opium consumption on cell proliferation and metastasis. In the next section, we are going to review the evidence on the association between opium consumption and cancer and the biological basis for such an association.

Laryngeal Cancer

A case-control study by Mousavi et al on 98 patients with laryngeal cancer and 312 age- and gender-matched controls showed the possible association between opium consumption and laryngeal cancer. By adjusting for potential confounders, they demonstrated that use of opium was strongly associated with laryngeal cancer (OR = 10.74, 95% CI = 5.76 to 20.02; $P < 0.002$).[51] Rahmati et al performed an analysis on data from the Golestan Cohort Study to investigate the relationship between opium consumption and mortality from respiratory malignancies. The results demonstrated that after adjustment for age, sex, residential place, education level, marital status, alcohol use, and the cumulative use of any type of tobacco, opium consumption was associated with an increased risk of laryngeal cancer, very close to significance, with lower bounds of CIs being 0.99.[52] Bakhshaee et al evaluated the association between opium addiction and the risk of laryngeal carcinoma and found that the crude OR for laryngeal cancer in opium users was 9.09 (95% CI = 3.21 to 25.64; $P = 0.000$) relative to nonusers. Additionally, after adjustment for opium consumption with cigarette smoking, the OR for laryngeal cancer in opium users was 6.06 (95% CI = 1.10 to 33.23; $P = 0.05$). Laryngeal cancer was also detected in younger patients with opium dependency (54.54 ± 10.93; $P = 0.02$).[53] More recently, Sheikh et al performed an analysis on data from the Golestan Cohort Study to evaluate opium use and the subsequent incidence of cancer. They reported that the use of opium was associated with an increased risk of developing laryngeal cancer (HR = 2.53, 95% CI = 1.21 to 5.30; $P < 0.05$).[54] Table 3 demonstrates all studies performed on this topic and a summary of other studies on the association between opium consumption and cancer.

Lung Cancer

Lung cancer is well-known to be the most prevalent malignancy and the leading cause of mortality in the world. The results of a study by Rahmati et al on data from the Golestan Cohort Study showed that opium consumption was associated with an increased rate of lung cancer mortality (OR = 1.96; 95% CI = 1.18 to 3.25). The long-term use of opium also showed an increased rate of death due to respiratory malignancies (HR = 3.01; 95% CI = 1.55 to 5.81).[52] In another analysis based on the Golestan Cohort Study, Sheikh et al investigated 1833 participants diagnosed with cancer during a median follow-up of 10 years and reported that opium use was associated with increased incidence of lung cancer (HR = 2.21, 95% CI = 1.44 to 3.39; $P < 0.05$).[54]

Esophageal Cancer

Several reports have indicated a positive association between opium consumption and esophageal cancer with a dominant type of squamous cell carcinoma (ESCC). Ghadirian et al performed a case-control study on 82 patients to evaluate the association between the presence of morphine metabolites and esophageal cancer. They found that individuals with more than 1 μg/mL of morphine metabolites in their urine had a higher rate of esophageal cancer.[55] Bakhshaie et al also performed a case-control study to evaluate the association between the risk of esophageal carcinoma and opium addiction. They demonstrated that the crude OR for esophageal cancer was 1.44 (95% CI = 0.57 to 3.62; $P = 0.43$) relative to nonusers.[53] Other studies conducted on the population in the northern Iranian province of Golestan are known for a high incidence of esophageal cancer. In their case-control study, Nasrollahzadeh et al observed that 30% of patients with ESCC and 18% of controls were opium users. More interestingly, the authors observed an even stronger association between using *shireh* and ESCC than between

Table 3. Summary of Studies Evaluating the Association Between Opium Consumption and Cancer and its Outcomes

Study Reference	Type of Study	Study Population	Measured Outcome	Result
Oral cancer				
Razmpa et al., 2014 [76]	Case-control	160 individuals (80 patients with oral cavity cancer)	Cancer incidence	Opium consumption was significantly related to oral cavity cancer (OR = 4.0; 95% CI = 1.2 to 13.6).
Laryngeal cancer				
Mousavi et al., 2003 [51]	Case-control	N = 410 (98 patients with laryngeal cancer and 312 cancer-free subjects)	Cancer prevalence	Opium consumption was a factor for laryngeal cancer with a crude OR of 21.55 (95% CI = 10.54 to 44; $P < 0.001$). The adjusted odds ratio showed that opium was strongly associated with laryngeal cancer (OR = 10.74; 95% CI = 5.76 to 20.02; $P < 0.0021$).
Rahmati et al., 2017 [52]	Cohort	N = 50045 (8487 opium users and 43 mortality cases due to respiratory malignancies)	Cancer mortality	Opium consumption was almost significantly associated with an increased risk of laryngeal cancer (95% CI: 0.99).
Bakhshaee et al., 2017 [53]	Case-control	N = 181 (58 cases with laryngeal cancer and 98 cases with esophageal cancer)	Cancer prevalence	The crude OR for laryngeal cancer in opium users was 9.09 (95% CI = 3.21 to 25.64; $P = 0.000$) compared to nonusers. After adjustments for opium with cigarette smoking, the OR for laryngeal cancer in opium users was 6.06 (95% CI = 1.10 to 33.23; $P = 0.05$). Laryngeal cancer was also discovered in younger patients with opium dependency (54.54 ± 10.93; $P = 0.02$).
Sheikh et al., 2020 [54]	Cohort	N = 50045 (8487 opium users and 1833 cases with cancer)	Cancer incidence	The use of opium was associated with an increased risk of developing laryngeal cancer (HR = 2.53, 95% CI = 1.21 to 5.30; $P < 0.05$).
Lung cancer				
Rahmati et al., 2017 [52]	Cohort	N = 50045 (8487 opium users and 43 mortality cases due to respiratory malignancies)	Cancer mortality	Opium consumption was almost significantly associated with an increased risk of lung cancer (OR = 1.73; 95% CI = 0.99 to 3.03).
Sheikh et al., 2020 [54]	Cohort	N = 50045 (8487 opium users and 1833 cases with cancer)	Cancer incidence	Opium consumption was associated with an increased risk of developing lung cancer (HR = 2.21, 95% CI = 1.44 to 3.39; $P < 0.05$).
Esophageal cancer				
Ghadirian et al., 1985 [55]	Case-control	N = 41 cases and 41 controls	Cancer prevalence	Individuals with more than 1 µg/mL of morphine metabolites in their urine had a higher rate of esophageal cancer.
Nasrollahzadeh et al., 2008 [56]	Case-control	N = 871 (300 cases with ESCC and 571 cancer-free cases)	Cancer prevalence	Consuming shireh had a stronger association with ESCC than consuming usual opium (OR = 3.41; 95% CI = 1.35 to 8.60, and OR = 1.62; 95% CI = 1.09-2 to 40, respectively). Opium use and ESCC had a dose-response relationship.
Malekzadeh et al., 2013 [57]	Cohort	N = 50045 (8487 opium users and 134 cases of GI mortality due to ESCC)	Cancer mortality	After adjustments for potential confounders and exclusion of those who started opium use after major chronic illnesses, the use of opium was associated with a 69% increase in the risk of ESCC-related mortality (HR = 1.69, 95% CI = 1.11 to 2.56; $P = 0.035$).
Bakhshaee et al., 2017 [53]	Case-control	N = 181 (58 cases with laryngeal cancer and 98 cases with esophageal cancer)	Cancer prevalence	The crude OR for esophageal cancer was 1.44 (95% CI = 0.57 to 3.62; $P = 0.43$) in opium users compared to nonusers.
Sheikh et al., 2019 [58]	Cohort	N = 50045 (8487 opium users)	Cancer incidence	After adjustments for potential confounders such as age, gender, residence districts, ethnicity, and quartiles of the socioeconomic status, the results showed that smoking opium was associated with an increased risk of ESCC (HR = 1.85, 95% CI = 1.18 to 2.90; $P = 0.009$).
Sheikh et al., 2020 [54]	Cohort	N = 50045 (8487 opium users and 1833 cases with cancer)	Cancer incidence	The use of opium was associated with an increased risk of developing esophageal cancer (HR = 1.38, 95% CI = 1.06 to 1.80; $P < 0.05$).
Gastric Adenocarcinoma				
Malekzadeh et al., 2013 [57]	Cohort	N = 50045 (8487 opium users and 125 cases with GI mortality due to gastric cancer)	Cancer mortality	After adjustments for possible confounding variables and exclusion of those who started opium use after major chronic illnesses, the use of opium was associated with a 22% increase in the risk of gastric-related mortality (HR = 1.22; 95% CI = 0.79 to 1.89).
Shakeri et al., 2013 [59]	Case-control	N = 922 (309 cases of gastric adenocarcinoma and 613 matched controls)	Cancer prevalence	Opium increased the risk of all types of adenocarcinoma (OR = 3.1; 95% CI = 1.9 to 5.2). Opium consumption after a diagnosis of gastric cancer showed a significant increase in all types of gastric cancer (OR = 2.9; 95% CI = 1.7 to 4.8). Patients with the highest cumulative opium consumption demonstrated the potent relationship (OR = 4.5; 95% CI = 2.3 to 8.5).
Sadjadi et al., 2014 [60]	Cohort	N = 928 Helicobacter-positive patients	Cancer incidence	Opium use increased the risk of all gastric cancers (HR = 3.2; 95% CI = 1.4 to 7.7).
Sheikh et al., 2020 [54]	Cohort	N = 50 045 (8487 opium users and 1833 cases with cancer)	Cancer incidence	The use of opium was associated with an increased risk of developing gastric cancer (HR = 1.36, 95% CI = 1.03 to 1.79; $P < 0.05$).

Table 3. Continued

Study Reference	Type of Study	Study Population	Measured Outcome	Result
		Pancreatic Cancer		
Shakeri et al., 2016 [61]	Case-control	N = 685 (357 patients with pancreatic cancer and 328 cancer-free subjects)	Cancer prevalence	After adjustments for opium consumption with potential confounders such as age and the duration and cumulative use of opium, the results demonstrated a significant relationship between opium and pancreatic cancer without a dose-response relationship (OR = 1.91; 95% CI = 1.06 to 3.43).
Moossavi et al., 2018 [62]	Cohort	N = 50045 (54 cases with pancreatic cancer)	Cancer incidence	High cumulative use of opium in comparison with the never use was strongly associated with pancreatic cancer even after adjustments for age, sex, cigarette smoking, obesity, diabetes mellitus, and alcohol (HR = 3.56, 95% CI = 1.49 to 8.50; $P = 0.090$).
		Colorectal Carcinoma		
Naghibzadeh-Tahami et al., 2016 [63]	Case-control	N = 525 (175 cases with CRC and 350 cancer-free subjects)	Cancer prevalence	Opium consumption was associated with an increased risk of CRCs (adjusted OR = 4.5; 95% CI = 2.4 to 8.7). A dose-response relationship was noticed between the cumulative use of opium and the incidence of CRCs (low use OR = 3.7; 95% CI = 1.5 to 8.6, and high use OR = 8.0; 95% CI = 2.9 to 21.7).
Dianatinasab et al., 2016 [64]	Cohort	N = 220 CRCs	Cancer mortality	Opium consumption was significantly correlated with a higher risk of colorectal cancer-related death (HR = 2.49, 95% CI = 1.41 to 4.42; $P = 0.001$).
		Bladder Cancer		
Sadeghi et al., 1979 [65]	Case-control	N = 189 (99 cases with bladder cancer)	Cancer prevalence	A high correlation was observed between opium addiction and bladder cancer.
Aliasgari et al., 2004 [66]	Case-control	N = 160 (52 cases and 108 controls)	Cancer prevalence	Smoking cigarettes and opium usage increased the risk of BC (OR = 6.2; 95% CI = 2.04 to 8.70).
Ketabchi et al., 2005 [67]	Case-control	N = 242 (112 cases and 130 controls)	Cancer prevalence	The amount, duration, and methods of opium consumption could be related to BC. The risk ratio associated with opium use was 8 (OR = 7.99, 95% CI = 5.3 to 12.5; $P = 0.0001$).
Nourbakhsh et al., 2006 [68]	Case-control	N = 510 (255 cases and 255 controls)	Cancer prevalence	Opium was a risk factor for transitional-cell carcinoma (OR = 3.88, 95% CI = 1.99 to 7.57; $P = 0.001$).
Shakhssalim et al., 2010 [69]	Case-control	N = 912 (418 cases and 494 controls)	Cancer prevalence	Opium could be an important factor in developing transitional cell carcinoma ($P = 0.0001$). The risk ratio associated with opium use was 2.6 (95% CI = 1.6 to 4.3).
Hosseini et al., 2010 [70]	Case-control	N = 358 (179 cases with BC and 179 cancer-free subjects)	Cancer prevalence	Opium consumption was associated with a significantly increased rate of BC (OR = 4.6, 95% CI = 3.5 to 6.3; $P < 0.001$). There was a synergistic association between heavy cigarette smoking and opium consumption concerning BC occurrence (OR = 6.16; 95% CI = 3.34 to 8.32; $P = 0.0001$).
Ghadimi et al., 2015 [72]	Case-control	N = 304 (152 cases and 152 controls)	Cancer prevalence	Opium abuse individually was associated with bladder cancer. The OR for opium was 4.96 (95% CI = 1.07 to 22.92).
Alimarji et al., 2015 [71]	Case-control	N = 350 (175 cases and 175 controls)	Cancer prevalence	A significant association was observed between smoking, opium consumption, and an increased risk of BC ($P < 0.001$).
Akbari et al., 2015 [74]	Case-control	N = 533 (155 cases with BC and 378 cancer-free subjects)	Cancer prevalence	A significant relationship was observed between opium usage and BC after adjustments for potential confounders including nutritional factors, alcohol, and tobacco (OR = 3.9; 95% CI = 1.3 to 12.0) in a dose-response manner (OR = 4.9; 95% CI = 1.1 to 21.9).
Lotfi et al., 2016 [75]	Case-control	N = 400 (200 cases with BC and 200 cancer-free subjects)	Cancer prevalence	Opium consumption was associated with an increased risk of BC (OR = 3.01, 95% CI = 1.73 to 5.23; $P < 0.0001$).
Afshari et al., 2017 [73]	Systematic review and meta-analysis	17 studies	Cancer prevalence	The OR for the association between BC and opium use (without cigarette smoking) was 3.85 (95% CI = 3.05 to 4.87), while it increased to 5.7 (95% CI = 1.9 to 16.3) with cigarette smoking.
Sheikh et al., 2020 [54]	Cohort	N = 50045 (8487 opium users and 1833 cases with cancer)	Cancer incidence	The use of opium was associated with an increased risk of advancing bladder cancer (HR = 2.86, 95% CI = 1.47 to 5.55; $P < 0.05$).

OR, odds ratio; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; ESCC, esophageal squamous cell carcinoma; CRC: colorectal carcinoma; BC: bladder cancer.

usual opium and ESCC (OR = 3.41; 95% CI = 1.35 to 8.60 and OR = 1.62; 95% CI = 1.09 to 2.40, respectively).[56] These results were further supported and expanded by the Golestan Cohort Study, which demonstrated that after adjustment for potential confounding variables and the exclusion of those who started opium consumption in the wake of a major chronic disease (including CAD, stroke, diabetes mellitus, and hypertension), the use of opium was related with a 69% increased risk of ESCC-related mortality (HR = 1.69; 95% CI = 1.11 to 2.56) in a dose-dependent manner.[57] Another report of the Golestan Cohort Study demonstrated that, after adjustments for potential variables including age, gender, residence districts, ethnicity, and quartiles of the socioeconomic status, opium use was associated with a dose-response increased risk of ESCC (HR = 1.85; 95% CI = 1.18 to 2.90; $P = 0.009$).[58] A more recent analysis of their data also showed that opium use was associated with a

risk of developing esophageal cancer (HR = 1.38, 95% CI = 1.06 to 1.80; $P < 0.05$), dose-dependently.[54] Studies are summarized in Table 3.

Gastric Adenocarcinomas

Different investigations have shown a strong relationship between opium use and gastrointestinal tract carcinoma, which counts as the second cause of cancer-related mortality worldwide and the most common cause of cancer in Iran. For instance, an analysis of the Golestan Cohort Study by Malekzadeh et al showed that the use of opium was associated with a 22% increase in the risk of gastric-related mortality (HR = 1.22; 95% CI = 0.79 to 1.89).[57] In another case-control study in the Golestan Province of Iran, Shakeri et al evaluated 922 patients (309 cases of gastric adenocarcinoma) and demonstrated that opium consumption after the diagnosis of gastric cancer exhibited a significant rise in all types of gastric cancer (OR = 2.9; 95% CI = 1.7 to 4.8). Moreover, those with the highest cumulative opium consumption showed the strongest relationship (OR = 4.5; 95% CI = 2.3 to 8.5).[59] Sadjadi et al performed a cohort study on 928 Helicobacter-positive patients and observed that opium use was significantly associated with baseline antral and body intestinal metaplasia (OR = 3.2, 95% CI = 1.2 to 9.1; $P = 0.022$ and OR = 7.3, 95% CI = 2.5 to 21.5; $P = 0.001$, respectively). Opium use increased the prevalence of all gastric cancers (HR = 3.2; 95% CI = 1.4 to 7.7).[60] Sheikh et al performed another analysis from the Golestan Cohort Study to evaluate the association between opium consumption and developing gastric carcinoma. They found that the use of opium was associated with an increased risk of the development of gastric cancer (HR = 1.36, 95% CI = 1.03 to 1.79; $P < 0.05$).[54]

Pancreatic Cancer

Shakeri and colleagues observed that after adjustment for potential confounding variables including age and the duration and cumulative use of opium, a relationship was observed between opium consumption and the risk of pancreatic cancer (OR = 1.91; 95% CI = 1.06 to 3.43) without a dose-response relationship.[61] In an analysis of the Golestan Cohort Study, Moossavi and colleagues identified a greater effect of opium ingestion (HR = 2.38, 95% CI = 1.00 to 5.69; $P = 0.05$) in comparison to its inhalation (HR = 1.88; 95% CI = 0.91 to 3.89) on the incidence of pancreatic cancer. After adjustment for the cumulative dose of cigarette smoking, the authors also detected that high cumulative use of opium was significantly associated with the risk of pancreatic cancer (HR = 3.56, 95% CI = 1.49 to 8.50; $P = 0.090$).[62]

Colorectal Carcinomas

A few studies have explored the association between opium consumption and colorectal carcinomas (CRCs), including colon, rectum, and anus cancers. Naghibzadeh-Tahami et al conducted a case-control study on 175 patients with CRC and 350 healthy individuals to observe any possible association between opium consumption and the incidence of CRCs. They demonstrated that opium and its derivatives were associated with an increased risk of all CRCs (OR = 4.5; 95% CI = 2.4 to 8.7) and colon cancers (OR = 5.7; 95% CI = 2.7 to 11.9). They observed strong relationships between the daily dose and the duration of opium consumption and CRCs and colon cancers.[63] Dianatinasab et al performed a prospective cohort study on 220 patients with CRCs to determine their mortality rate. They demonstrated that opium consumption was significantly associated with a higher risk of CRC-related mortality (HR = 2.49, 95% CI = 1.41 to 4.42; $P = 0.001$).[64]

Bladder Cancer

Sadeghi et al were the first to perform a case-control study on 189 patients in Iran to demonstrate a correlation between opium addiction and bladder cancer.[65] Afterwards, many investigators reported such an association between opium consumption and bladder cancer[66-77] (Table 3). The dominant histological type was transitional-cell carcinoma in most of the studies. Akbari et al observed a significant relationship between opium consumption and the prevalence of bladder cancer after adjustment for potential confounding variables including nutritional factors and tobacco use (OR = 3.9; 95% CI = 1.3 to 12.0). Additionally, they observed a significant dose-response relationship between opium use and bladder cancer (OR = 4.9; 95% CI = 1.1 to 21.9).[74] Opium has been demonstrated to have a deleterious effect on cell survival insofar as it increases the metastasis of cells in the urinary system. A systematic-review and meta-analysis was conducted by Afshari and colleagues to evaluate the association between opium consumption and the development of bladder cancer. The OR for the association between bladder cancer and opium use (without cigarette smoking) was 3.85 (95% CI = 3.05 to 4.87), which increased to 5.7 (95% CI = 1.9 to 16.3) when both opium use and cigarette smoking were examined.[73] Another analysis of the Golestan Cohort Study demonstrated a significant association between opium consumption and bladder cancer (HR = 2.86, 95% CI = 1.47 to 5.55; $P < 0.05$).[54]

Other Types of Cancer

Razmpa and colleagues evaluated the connection between opium use and oral cavity cancer in 160 individuals (80 patients with oral cavity cancer). They demonstrated that opium consumption was significantly related to oral cavity cancer (OR = 4.0; 95% CI = 1.2 to 13.6).[76]

The Shared Role of Opium in the Pathogenesis of ASCVD and Cancer

Inflammation

It is well known that chronic low-grade inflammation has a pivotal role in the formation of atherosclerotic plaques and their progression. Atherosclerotic plaques contain many pro-inflammatory cytokines such as C-reactive protein

(CRP), interleukin-1 (IL-1), tumor necrosis factor-α, and interferon-γ (INF- γ)[77] that accelerate atherogenesis. This lipid-rich, inflamed microenvironment of plaques also contains reactive oxygen species (ROS) and oxidized low-density-lipoprotein cholesterol, causing increased inflammatory signaling, foam cell formation, and angiogenesis.

Rudolf Virchow in the 19th century claimed that there was a link between inflammation and cancer.[78] He found that several solid cancers were triggered by chronic inflammatory state, inflamed environments, and interactions of mediators.[1] Tumor growth depends on the activation of a wide range of pathways such as Janus-activated kinase, mitogen-activated protein kinase, and protein kinase B that can progress the carcinogenesis of affected cells and promote malignancy by the transcriptional activation of pro-inflammatory, pro-survival, and proteolytic programs via the signal transducer and activator of transcription, nuclear factor-kB, and hypoxia-inducible factor-1α.[78-82] Furthermore, ROS and subsequent reactive nitrogen species can stimulate DNA destruction and resultant mutations in oncogenes and tumor suppressor genes could result in carcinogenesis.[81,82]

In conclusion, inflammation and oxidative stress have an important part in the pathogenesis of both CVD and cancer. Recent studies have shown that chronic exposure to opium enhances the levels of pro-inflammatory mediators including CRP, IL-17, IL-6, INF-γ, IL-1 receptor antagonist, and C3 and C4 complement factors and decreases the levels of cytokines like transforming growth factor-β.[83-85] Hence, chronic exposure to opium could initiate/accelerate atherogenesis and carcinogenesis by enhancing inflammation and oxidative stress.

Plasminogen Activator Inhibitor-1

Plasminogen activator inhibitor-1 (PAI-1) accounts as an inhibitor of fibrinolysis.[86] There is accumulating evidence that PAI-1 is involved in atherogenesis; its activation promotes thrombus formation, stabilizes the fibrin matrix, and stimulates vascular smooth muscle cell proliferation and low-density lipoprotein uptake into the plaque.[87,88] Additionally, it has been shown that levels of PAI-1 are increased in individuals with various types of cancer[86,89-92] and predict worse prognoses.[93-95] Recent studies have demonstrated that levels of PAI-1 are higher in opium addicts than nonusers. More interestingly, there is evidence that opioid receptors are present on various cancer cell types and the main alkaloids of opium-like morphine could upregulate the expression of the *PAI-1* gene and, therefore, increase the progression of tumor cells.[96] Hence, it could explain, at least in part, the increased risk of atherosclerosis and cancer in opium users.

Adipokine (Adiponectin)

Adiponectin is a unique adipokine which has beneficial metabolic properties including anti-inflammatory, anti-oxidant, anti- or pro-atherogenic, and insulin sensitizing effects. It is a potential prognostic biomarker and a therapeutic target for patients with CVD that have atherosclerosis, inflammation, and insulin resistance.[97] Moreover, evidence proposes that adiponectin may have connection with the pathogenesis of several malignancies and their poor prognoses.[98] Generally, serum adiponectin levels are reduced in various cancers, including breast,[99] endometrial,[100] CRC,[101] hematologic,[102] pancreatic,[103] lung,[104] prostate,[105] esophageal,[106] and gastric[106] cancer. A recent investigation has shown that the adiponectin level is lower in opium consumers than in no consumers.[107] The decreased levels of adiponectin could explain, at least in part, the increased risk of CVD occurrence and cancer in opium users.

Homocysteine

Hyperhomocysteinemia is known to be an independent risk factor for ASCVD.[108-112] Homocysteine can cause vascular lesion, atherogenesis, thrombogenesis, hyperplasia, endothelial dysfunction, decreased nitric oxide and stimulating vascular smooth muscle cell proliferation.[109,113] Recent studies have also proven that there is a close link between hyperhomocystinuria and cancer and it is a novel potential tumor biomarker.[114] Moreover, several polymorphisms in the enzymes involved in the homocysteine detoxification pathways have close clinical ties to several cancer types, such as breast,[115] CRC,[116] acute lymphoblastic leukemia[117] and prostate.[118] Masoomi et al demonstrated that opium consumption was strongly accompanied by increased levels of homocysteine, which could explain the increased incidence of CVD and cancer in opium users.[119]

Fibrinogen

Fibrinogen is an independent risk factor for ASCVD.[120] Increased levels of fibrinogen are associated with the development of ASCVD through platelet aggregation, fibrin formation, atherosclerotic plaque evolution, and thrombus formation.[121-123] In a few recent studies, convincing evidence has been provided to demonstrate that plasma fibrinogen is associated with tumor progression and poor prognoses in lung,[124] breast,[125] gastric.[126] ovarian,[127] oral and oropharyngeal,[128] biliary tract,[129,130] and penile cancer. Fibrinogen/fibrin seems to simplify the microvascular entrapment necessary for metastasis and to contribute to the formation of the connective tissue (stroma) of some forms of solid tumor.[131,132] There is evidence that opium consumption is associated with increased levels of clotting factors such as fibrinogen, explaining partially the increased risk of cancer development and ASCVD in opium users.[133,134]

HbA1c

HbA1c is a well-known marker of long-term glycemic control in patients with diabetes mellitus, and elevated HbA1c levels are correlated with an increased risk for future microvascular and macrovascular disease. A few

studies have shown HbA1c to be predictive of CAD in nondiabetics and to be correlated with the severity of CAD.[135,136] Furthermore, evidence also suggests that elevated HbA1c is related with an increased risk of developing certain types of cancer compared with nondiabetics, with the strongest associations seen with hepatic, pancreatic, endometrial, renal, breast, esophageal, colorectal, and bladder cancer.[137] Recently, contrary to the traditional belief that opium consumption decreases blood glucose and insulin resistance, it has been found that HbA1c is higher in opium users than in nonusers.[11,16,133] Hence, it could also justify the increased risk of ASCVD and cancer in opium users.

Factor VII

Factor VII (FVII) contributes to the initiation of the extrinsic pathway by binding to tissue factor. Coagulation cascade and platelet activation and subsequent acute coronary events is led by the formation of the FVII complex.[138,139] Additionally, mounting evidence suggests that the tissue factor-FVII complex is involved in pathophysiological processes of cancer development, including angiogenesis, tumor migration and invasion, and cell survival.[138,140,141] Asgary et al demonstrated that opium users had higher levels of FVII than nonusers, which could also explain the higher risk of ASCVD and cancer in opium users.[133]

Limitations of Studies on the Association Between Opium and ASCVD and Cancer

As we reviewed in previous sections and summarized in tables, the majority of the studies evaluating the association between opium consumption and ASCVD and cancer have case-control or cross-sectional designs. Case-control studies are excellent for studying rare/non-prevalent diseases such as cancer; however, they carry some inherent limitations that call for attention when interpreting their results. Although case-control clinical studies have demonstrated the relationship between opium consumption CAD, stroke, and cancer, we cannot make a causative interpretation because the temporal relationship between opium consumption and ASCVD or cancer cannot be determined in these studies. Indeed, it is likely that some people with ASCVD, stroke, or cancer start consuming opium due to their symptoms/belief about the advantageous effects of opium use on ASCVD or cancer following the development of their disease. Thus, as we witness a higher prevalence of opium usage among patients with ASCVD or cancer than among normal controls, we cannot make a causal interpretation. Despite the high prevalence of opium consumption among Eastern people, opium carries a stigma for the individual and its reporting varies between patients and healthy individuals. It is expected that healthy individuals within the control group under-report their opium consumption that would result in the overestimation of the outcomes of opium consumption on the development of ASCVD or cancer. Nonetheless, cohort studies can overcome the limitation of temporality and unbalanced reporting of exposure to opium. Fortunately, almost all of the aforementioned concerns have been regarded and minimized thanks to the results of the Golestan Cohort Study.

In conclusion, although ASCVD and cancer are seemingly different types of disease, they have multiple shared pathogenesis mechanisms and lifestyle-related risk factors like smoking, unhealthy diet, excessive alcohol consumption, and inadequate physical activity. We believe that opium consumption should be added to the current list of the lifestyle-related shared risk factors of ASCVD and cancer and special strategies should be developed and conducted for more comprehensive joint preventive programs that target both top-ranking killers in the world.

Authors' Contribution

FM and NS generated the idea of a review article. FM and NY drafted the article. RM, KZ, AM, AVF, AI, MT, PR, KTA, and NS edited the manuscript independently and made critical scientific revisions.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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