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Opium Use and Risk of Mortality from Digestive Diseases -- A Prospective Cohort Study

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Abstract

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Background—Opium use, particularly in low doses, is a common practice among adults in northeastern Iran. We aimed to investigate the association between opium use and subsequent mortality from disorders of the digestive tract.

Methods—We used data from the Golestan Cohort Study (GCS), a prospective cohort study in northeastern Iran, with detailed, validated data on opium use and several other exposures. A total of 50,045 adults were enrolled during a four-year period (2004–2008) and followed annually until December 2012, with a follow-up success rate of 99%. We used Cox proportional hazard regression models to evaluate the association between opium use and outcomes of interest.

Results—8,487 (17%) participants reported opium use, with a mean duration of 12.7 years. During the follow-up period 474 deaths from digestive diseases were reported (387 due to gastrointestinal cancers and 87 due to nonmalignant etiologies). Opium use was associated with an increased risk of death from any digestive disease (adjusted hazard ratio (HR) = 1.55, 95% CI 1.24 – 1.93). The association was dose-dependent, with a HR of 2.21 (1.57–3.31) for the highest quintile of cumulative opium use vs. no use ($P_{\text{trend}} = 0.037$). The hazard ratios (95% CI) for the associations between opium use and malignant and nonmalignant causes of digestive mortality were 1.38 (1.07 – 1.76) and 2.60 (1.57 – 4.31), respectively. Increased risks were seen both for smoking opium and for ingestion of opium.

Conclusion—Long-term opium use, even in low doses, is associated with increased risk of death from both malignant and nonmalignant digestive diseases.

Introduction

Opium is the air-dried extract of the opium poppy, *Papaver somniferum*. This extract includes a large number of molecules, including narcotic alkaloids (e.g., morphine and codeine), non-narcotic alkaloids (e.g., papaverine, thebaine, and noscapine), and non-alkaloids (e.g., sugars and meconic acid).(1) These compounds may affect human physiology and health in many different ways, the totality of which could only be assessed in long-term human studies.

Opium has long been used for medical and recreational purposes in many parts of the world, including Iran. Avicenna's 10th century article was the main reference for medicinal use of opium until the 19th century.(2) A combination of criminalization of opium use, as well as availability of other psychoactive drugs such as cannabis, has resulted in lower use of opium in the developed world. Yet opium is still commonly used in other parts of the world, mainly in Western and Central Asia.(1) Globally, an estimated 13 to 22 million people, mostly from Asian countries, consumed opium and its derivatives in 2008.(3)

A popular belief among lay people, and even perhaps among the older generation of physicians in Western and Central Asia, is that long-term use of low dose opium can prolong survival by preventing chronic diseases such as diabetes mellitus, cardiovascular diseases, and cancer. However, published data do not support this hypothesis. Several case-control studies and case-series have suggested deleterious effects of opium consumption, associating its use with higher risk of cardiovascular outcomes and a variety of cancers.(4–14) A recent report from the Golestan Cohort Study showed that opium use, even in low doses, was associated with a near doubling of all-cause mortality.(15)

Opiates are metabolized principally in the liver, and chronic ingestion of morphine in mice has been shown to cause histopathological changes in the liver resulting in abnormal liver function tests.(16) In humans, long-term use of opiates, particularly morphine, can commonly cause constipation, which results from opium's disruption of neurotransmission in the enteric nervous system, leading to decreased motility and decreased secretion of water, electrolytes and bile in the GI tract.(17) Thus opium use may be involved in the etiology of multiple digestive tract disorders. Several studies have reported an association between opium use and esophageal cancer(4, 18, 19) or gastric cancer,(20, 21) but no study has reported on the association between opium use and all digestive disease-related mortality, including deaths from diseases with nonmalignant etiologies. We conducted this study to investigate the association between opium use and mortality due to gastrointestinal and liver diseases.

Methods

Study population

The Golestan Cohort Study (GCS) is a prospective cohort study of 50,045 adults, aged 40 to 75 years, from Golestan province of Iran who were recruited between January 2004 and June 2008. A detailed description of this study is available elsewhere.(22, 23) In summary, a total of 10,033 participants were enrolled from Gonbad City, the largest city in the study area, with participation rates of approximately 70% and 50% for women and men, respectively. In addition, 40,012 participants were enrolled from 326 villages, with participation rates of 84% for women and 70% for men. Figure 1 shows the flow chart of study recruitment. Seventy-five percent of the study participants were Turkmen ethnics, who likely descended from Turkic tribes and migrated from the Altai Mountains on the border of China and Mongolia to northern Iran. Turkmens present live in Turkmenistan (part of the Ancient Iranian Empire) and northeastern Iran, primarily in Golestan province.

Opium use was assessed using a structured questionnaire, which included detailed questions about the age of starting opium use, daily amount and frequency of use (how many days a week if weekly or more), routes of intake, opium types (teriak, sukhteh, shireh, and heroin), (15) and the age of quitting consumption, if the person had quit. If subjects used several types of opium, or they used opium intermittently (stopped and resumed use), data were recorded separately for each type and period of use. The accuracy of self-reported opium use in this population has been evaluated by comparing the presence of codeine or morphine in urine samples of 150 cohort participants with self-reported opium use. That study showed a relatively high accuracy for self-report of opium use in these cohort participants, with a sensitivity of 0.93 and a specificity of 0.89.(24) The GCS methods were approved by the ethical review boards of Digestive Disease Research Center (DDRC), the International Agency for Research on Cancer (IARC), and the National Cancer Institute (NCI), and all participants signed a written informed consent at enrollment.

Cause of death ascertainment

The follow-up methods and cause of death ascertainment in the GCS have been described in detail elsewhere.(15, 25) In brief, the follow-up team uses several methods, including annual

phone calls to study participants, communicating with local health workers, and collecting data from local death registries and cancer registries, to either reach the study participants or to collect information on the occurrence and cause of death. All cohort participants are phoned annually and asked about vital status and any admission to a hospital or outpatient clinic, and the information is recorded. If the participant is not reached after seven phone calls made in a two-week period, friends or local health workers are contacted. Using these methods, the follow-up success rate so far is over 99%.

If a death is reported, the physician in the follow-up team uses a validated verbal autopsy questionnaire to interview the closest relative of the deceased.⁽²⁵⁾ In addition to administration of the verbal autopsy for each deceased participant, the follow-up team actively pursues and collects all available medical documents such as hospital charts, physician notes, electrocardiography reports, endoscopy results and pathology reports from all medical centers of Golestan province and the neighboring provinces. Verbal autopsies have been carried out for 100% of deaths, and additional medical documents have been collected for 65%. To ascertain the cause of death, two internists independently review all collected medical documents as well as the completed verbal autopsy questionnaire and make their own diagnosis, according to the ICD-10 coding system (international classification of diseases, 10th revision). If the two diagnoses are concordant, the diagnosis is made. In case of discordance, a third more experienced internist reviews all documents and the two initial diagnoses to make the final diagnosis. If a final diagnosis cannot be made for any reason, the cause of death is coded as “unknown”. For the purpose of this paper, consistent with a national survey in 2009,⁽²⁶⁾ we focused on main causes of gastrointestinal causes of death, both malignant and non-malignant. The major malignant causes of death were esophageal and gastric cancers, and to a lesser extent colorectal and pancreatic cancers. The major non-malignant cause of death was liver cirrhosis, and less frequently, other alcoholic liver disease, cholelithiasis, and other inflammatory liver diseases.

Statistical Analysis

Statistical analyses were conducted with STATA statistical software, version 11 (STATA Corp, College Station, TX). Standardized mortality rates (SMRs) were calculated using the World Population 2000 as the reference population. Age-adjusted relative risks (RRs) were obtained by dividing SMRs.

We fitted Cox proportional hazards regression models, with age as the timescale, to estimate hazard ratios and 95% confidence intervals for mortality due to digestive diseases in association with opium use. The proportional hazard assumption was verified using Schoenfeld residuals. Follow-up continued until loss to follow-up, death, or 17 December 2012, whichever came first. We also adjusted the Cox models for sex, ethnicity (Turkmen or other), place of residence (urban or rural), cigarette smoking (ever or never), alcohol consumption (ever or never) and hepatitis B virus (HBV) infection. Inclusion of other variables, including level of education, marital status, body mass index (BMI), history of diabetes, and consumption of fruits and vegetables did not have a material effect on the association between opium use and GI mortality. Therefore we did not include them in the

fully adjusted Cox models to avoid instability of the models due to non-event strata in some categories of those variables.

We defined participants as an ever opium user if they used opium at least once a week for at least six months. We additionally defined former opium users as participants who had reported quitting their habit at least one year before the enrollment. For current users, duration of use and cumulative use (defined as duration of use, in days, multiplied by daily amount of opium use, in nokhods, a local unit for opium consumption that weighs about 200 mg) were categorized into fifths to test for dose-response relationships. The opiate types that were included in the analyses were teriak (raw opium), sukhteh, shireh, and heroin. Sukhteh is the dry, black residue of smoked teriak, which sticks to the opium pipe. It can be scraped from the opium pipe and ingested. Shireh is a refined opium product often made by boiling a combination of opium and sukhteh in hot water and passing the solution through filters several times. We estimated hazard ratios stratified by routes of administration, which included opium smoking, ingestion, or both. We did not consider injection as a method of opium use because heroin, the only intravenous opiate used in the study area, was used by only a very small number of participants.

Sensitivity analysis to assess reverse causality, by excluding deaths occurring in the first 12 months of follow-up, was also conducted. The possibility of reverse causality was also addressed by excluding from analysis participants who reported starting opium use after being diagnosed with a major chronic disease, including coronary heart disease, cerebrovascular accidents, diabetes mellitus, and hypertension.

Results

At baseline, 17% (n=8,487) of the cohort participants reported ever opium use, with a mean duration of 12.7 years. During the follow-up period 474 deaths from digestive diseases were reported, including 387 due to malignant and 87 due to non-malignant causes. The median follow-up time was 6.3 years, during which a total number of 332 (0.7%) participants were lost to follow-up and 3,110 (6.2%) died.

Table 1 shows the distribution and age-adjusted relative risks of digestive disease-related mortality in several subgroups of cohort participants. Results are shown separately for malignant and non-malignant causes. For deaths related to gastrointestinal malignancies, male gender (RR=2.0), being of Turkmen ethnicity (RR=1.8), cigarette smoking (RR=3.0), and opium use (RR=1.8) were risk factors. For non-malignant digestive-disease related causes of death, male gender (RR=1.8), having university education (RR=6.0), alcohol consumption (RR=3.3), cigarette smoking (RR=2.4), and opium use (RR=3.0) were associated with increased risk.

After adjusting for potential confounders, ever opium use was associated with a 55% increased risk of all GI mortalities (HR = 1.55, 95% CI: 1.24 – 1.93; Table 2). The risk was greater for non-malignant (HR 2.60, 95% CI 1.57 – 4.31) than malignant causes (1.38, 95% CI 1.07 – 1.76; $P_{\text{heterogeneity}} = 0.035$). The risks for all digestive mortality and for malignant

causes appeared to be dose-dependent ($P_{\text{trend}} = 0.037$ and 0.030 , respectively), but no trend was observed for non-malignant causes of mortality ($P_{\text{trend}} = 0.73$).

The mortality hazard ratios by type of opium usage are also shown in Table 2. There was no evidence for heterogeneity of risk between teriak and shireh opium use for any of the mortality end points. Similarly the route of administration was not an important determinant of digestive disease mortality risk.

Table 3 shows the results for the major individual causes of GI mortality. The three most common causes of GI mortality were esophageal cancer, gastric cancer, and liver cirrhosis. Of these, the risk of esophageal cancer and cirrhosis were statistically significantly increased by opium use, whereas the risk of gastric cancer was not.

Table 3 also shows the results of the sensitivity analysis that excluded deaths which occurred in the first 12 months after enrollment. Although the hazard ratios were slightly shifted toward null, no major changes in the results were observed. Excluding participants who reported starting opium use after being diagnosed with a major chronic disease did not materially change the results. When we further adjusted the model for self-reported history of liver disease, we also found no major change in results. Of the 40 participants who reported a history of liver disease at enrollment, one died of liver cirrhosis, three died from other non-digestive disease-related causes, and 36 were still alive on the day of last follow-up report.

Cigarette smoking, alcohol consumption, and hepatitis B virus (HBV) infection are among the well-known risk factors for various types of GI diseases. Therefore, we compared the strength of associations of opium and these three other risk factors in relation to mortality from digestive diseases in our cohort study participants (Supplementary Table 1). HBV infection, with a HR (95% CI) of 1.76 ($1.34 - 2.32$) was the strongest risk factor, followed by opium use (1.55 , $1.24 - 1.93$) and cigarette smoking (1.43 , $1.12 - 1.82$). Alcohol consumption showed a non-significant inverse association with all-cause GI mortality (0.61 , $0.37 - 1.00$), which is similar to what has been found in areas of China which have a high-risk for esophageal and gastric cancer.⁽²⁷⁾ In these areas, alcohol consumers are relatively few, consume relatively little alcohol, and may come from different socioeconomic backgrounds.

Discussion

The results of this study, which are based on an average 6.3 years of follow-up of 50,045 individuals, showed that opium use was associated with statistically significant increased risks of all-cause GI mortality, malignant causes of GI mortality, and non-malignant causes of GI mortality. For all cause GI mortality ($n = 474$), the estimated increased risk was 55% after adjusting for a number of potential confounders, including age, sex, residential place, ethnicity, cigarette smoking, alcohol consumption, and HBV infection. Interestingly, the hazard ratio point estimate for the association between opium use and GI mortality (1.55) was slightly higher than that for cigarette smoking and GI mortality (1.43). A clear dose-response association was also found between opium use and all GI mortality. And after we

eliminated cases diagnosed within the first year of follow-up, opium use was still significantly associated with increased risk of GI mortality. The two main types of opium used in the area, teriak and shireh, were both associated with increased risk of GI mortality. Similarly, both major routes of use, smoking and ingestion, were associated with increased risk. When the results were stratified by malignant and non-malignant causes, higher risks of both categories were associated with opium use and the majority of the overall associations were upheld. However, although non-malignant causes were more strongly associated with opium use than malignant causes (hazard ratio of 2.60 vs. 1.38), it was only the malignant causes that showed an obvious dose-response relationship. When stratified further, among the more common causes of GI mortality, risks of esophageal cancer and cirrhosis, but not gastric cancer, were statistically significantly associated with opium use.

Our study showed a significant association between opium use and esophageal cancer mortality. It is important to know whether or not this association is causal. Possible explanations other than causality include reverse causality, confounding, selection bias, reporting bias, ascertainment bias, and random error.(28) To reduce the possibility of reverse causality, we excluded from analysis all those who died within one year of enrollment in the study, yet the results did not change substantially. In another sensitivity analysis, we excluded those who reported opium use after receiving the diagnosis of a major chronic disease, and again the results did not change. We also adjusted for all major potential confounders, including age, sex, and cigarette smoking. The possibility of selection bias is also unlikely, as all cases and controls were from the same cohort. And since the results were obtained from a cohort study, the possibility of reporting bias is also low. Ascertainment bias is unlikely, as diagnosis of esophageal and gastric cancers is relatively straightforward, and the physicians who reviewed the mortality cases had no preconceived idea that opium could increase the risk of mortality due to benign digestive diseases. Although there are relatively few studies on opium and GI diseases, our results are consistent with the previous literature, and therefore the possibility of random error is low. Epidemiologic studies in the 1970s began to study the effects of opium use on health.(5, 18, 29–31) Among these, a household case-control study by Ghadirian and colleagues suggested an increased risk of esophageal cancer associated with opium use.(5) Further case-control studies that have been conducted over the past decade have shown increased risk of esophageal cancer(4, 23) and gastric cancer(20) in relation to opium use. Our results add to the literature that esophageal cancer could be caused by opium use.

Our results showed a strong association between opium use and death from liver cirrhosis, even after adjustment for HBV infection. We also found a nearly three-fold increased risk of mortality from other non-malignant GI diseases in current opium users. Again, the question of causality is an important one. For reasons similar to those mentioned above, the possibility of selection or reporting bias is small. Only one person who died of cirrhosis had reported a history of liver disease before enrollment, which makes reverse causality unlikely. Other important causes of cirrhosis in Golestan province and throughout Iran are viral hepatitis(33) and nonalcoholic steatohepatitis (NASH), a condition that has shown an increasing incidence trend in recent years(26) and is associated with type-II diabetes, obesity and hyperlipidemia.(34) While alcohol consumption has been shown to be another major risk factor for liver cirrhosis, it has already been shown that alcohol drinking is very rare in

this area.(4, 23) After adjusting our models for sex, ethnicity, place of residence, cigarette smoking, alcohol consumption, and hepatitis B virus (HBV) infection, in addition to other potential confounders, the association between opium use and mortality due to cirrhosis remained significant. Finally, although the results of our study were statistically significant, future studies with similar results would be helpful to eliminate the possibility of random error.

Our results did not show a statistically significant association between opium use and gastric cancer deaths, which is unlike what has been shown in a case-control study from this area(20) and a small cohort conducted in Northwest of Iran.(21) This may be due to a lack of effect, or due to inadequate power to detect the association, as there were only 125 deaths from gastric cancer in this study. We also observed no association between opium use and deaths from other cancers.

Opiates have analgesic, expectorant, and antitussive properties, but may also slow peristalsis in the GI tract. Morphine is the most prevalent and important alkaloid in opium, comprising 15% of opium, and it is responsible for most of its harmful effects. Other alkaloids, like codeine (0.7 to 5 percent), and thebaine (0.1 to 2.5 percent) also have some deleterious effects.(2) In addition to the compounds present in raw opium, opium smoke and opium dross contain additional compounds formed during pyrolysis, including polycyclic aromatic hydrocarbons (PAH), heterocyclic aromatic hydrocarbons, primary aromatic amines, and N-nitrosamines, which are highly active mutagens and are thought to be the reason for the oncogenicity of opium.(4, 15, 18, 19, 31, 35–37)

Several mechanisms could be proposed for the adverse effect of opium on the liver. Morphine, like other opiate alkaloids, is metabolized principally in the liver, via conjugation with glucuronic acid.(38) Similar to other substances metabolized by the liver, morphine exposure may result in some levels of hepatotoxicity.(39) Extensive animal research has shown that morphine and morphine-like agents can increase liver enzymes and lead to perivenular and focal hepatocellular necrosis.(16, 40–42) In one study, chronic usage of morphine in albino rats increased inflammatory infiltration and focal parenchymal necrosis in the liver, in addition to an increase in the total lipid content of hepatocytes, leading to hepatic damage.(43) Furthermore, a growing body of knowledge suggests a pivotal role for GI microbiota in the etiology of some chronic diseases.(44, 45) Since opium has been shown to decrease the secretion of water, electrolytes and bile acids into the GI tract, and to significantly reduce GI motility,(17) it could cause considerable changes in GI microbiota, which could make opium users prone to both inflammatory and malignant diseases of the GI tract, as well as other chronic diseases.(44–47)

The adverse effects of opium on health are not limited to GI cancers or liver diseases.(1, 48, 49) Other cross-sectional or case-control studies and a large cohort study(15) have shown that opium use can increase the risk of lung cancer,(50) bladder cancer,(6–8, 51) cardiovascular diseases,(9–14) and respiratory diseases.(52–54)

Raw opium is a complex mixture containing three primary alkaloids of pharmacologic interest, morphine, codeine, and thebaine. The percentage of these alkaloids in raw opium

varies dramatically due to differences in processing, and their concentration tends to rise progressively as the latex dries. Thus, the inherent variability of raw opium makes it difficult to make a direct dosage comparison between use of opium and use of pharmaceutical opiates or synthetic opiates. In addition, this study primarily evaluated the recreational use of opium, by smoking or ingestion, and did not look directly at potential deleterious effects of therapeutic or palliative use of opioid derivatives in the management of chronic disease, including cancer and non-cancer pain. The results of this study are still relevant, however, to clinical practice in countries where recreational opium use is not widespread. There is now ample evidence in the literature that many patients in the United States, Canada, Australia and Europe who use long term prescribed opioids such as morphine, hydromorphone, codeine, and oxycodone for chronic non-cancer pain are also at increased risk of dying from digestive disease, cardiovascular disease, and cancer, like the opium users in Golestan.(55–63) A cohort study in United States has shown that in adults with arthritis, all-cause mortality is almost twice as high in patients prescribed opioids as in those prescribed non-steroidal anti-inflammatory drugs (NSAID).(55) A study from Canada also found that adults who are on long term prescribed opioids are more likely to die than a control population, and that deaths from overdose are not the main cause of this difference.(57, 58) And a study of 1,193 cases from Australia comparing methadone to heroin found that exposure to methadone was more deleterious than exposure to heroin (a more refined product) for several chronic diseases.(64, 65) The results of the current study are significant for physicians practicing throughout the world, including Western countries, because they add to the evidence that, although not completely understood, opioids have substantial risks for human health, and these risks are probably related to the considerable growth in deaths related to the increase in prescribed opioid use in recent years. Taking all of the evidence into consideration, whenever possible, it may be time to consider other choices (e.g. NSAIDs) for non-cancer chronic pain, which is a common medical problem across the globe.

In addition to increasing the risk of several chronic digestive disease, it is interesting that long term opioid use has also been shown to increase the rate of hair greying, advanced dental disease, psychiatric disorders and a relative reduction in circulating stem cell numbers, a finding which is associated with the human aging process. Possible pathways explaining negative effects of opioids on stem cells include interference with the cell cycle via P16 at the G1/S transition, immune disturbance due to cross-interference between toll-like receptor signaling and retinoic acid inducible protein-1 (RIG-I-like receptors; RLR's), and other pathways. Some of these molecular pathways are also known to be involved in the development and progression of chronic digestive disease, cardiovascular disease, and cancer.(63, 65, 66)

Our study has several strengths, including its large sample size, prospective design, minimal loss to follow-up,(22, 23) prior validation of exposures(24) and outcome measures,(25) and the availability of data to adjust for many potential confounders.(15, 23) We also used several methods to analyze whether the results were causal. Our study also has some limitations, such as possible outcome misclassification due to using verbal autopsy alone to ascertain the cause of death in 35% of the deaths.

In summary, the findings of this study suggest an increased risk of mortality due to malignant and non-malignant GI-related causes of death in opium users, compared to never users. Although the non-experimental design hampers making a strong causal conclusion for this increased risk, all analyses conducted in this study, as well as the results of other published studies, suggest that the association is indeed causal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Kalant H. Opium revisited: a brief review of its nature, composition, non-medical use and relative risks. *Addiction*. 1997; 92(3):267–77. [PubMed: 9219389]
2. Paul L, Schiff J. Opium and its alkaloids. *Am J Pharm Educ*. 2002; 66:186–94.
3. UNODC. World Drug Report 2010. United Nations Publication; 2010. Available from: <http://www.unodc.org/unodc/en/data-and-analysis/WDR-2010.html>
4. Nasrollahzadeh D, Kamangar F, Aghcheli K, et al. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. *Br J Cancer*. 2008; 98(11):1857–63. [PubMed: 18475303]
5. Ghadirian P, Stein GF, Gorodetzky C, et al. Oesophageal cancer studies in the Caspian littoral of Iran: some residual results, including opium use as a risk factor. *Int J Cancer*. 1985; 35(5):593–7. [PubMed: 3997280]
6. Aliasgari MA, Kaviani A, Gachkar L, et al. Is bladder cancer more common among opium addicts? *Urol J*. 2004; 1(4):253–5. [PubMed: 17914701]
7. Shakhssalim N, Hosseini SY, Basiri A, et al. Prominent bladder cancer risk factors in Iran. *Asian Pac J Cancer Prev*. 2010; 11(3):601–6. [PubMed: 21039023]
8. Hosseini SY, Safarinejad MR, Amini E, et al. Opium consumption and risk of bladder cancer: A case-control analysis. *Urol oncol*. 2010; 28(6):610–6. [PubMed: 19110453]
9. Masoumi M, Shahesmaeili A, Mirzazadeh A, et al. Opium addiction and severity of coronary artery disease: a case-control study. *J Res Med Sci*. 2010; 15(1):27–32. [PubMed: 21526055]
10. Masoomi M, Ramezani MA, Shahriari S, et al. Is opium addiction a risk factor for deep vein thrombosis? A case-control study. *Blood coagul fibrinolysis*. 2010; 21(2):109–12. [PubMed: 20083999]
11. Sadeghian S, Darvish S, Davoodi G, et al. The association of opium with coronary artery disease. *Eur J Cardiovasc Prev Rehabil*. 2007; 14(5):715–7. [PubMed: 17925633]

12. Sadeghian S, Graili P, Salarifar M, et al. Opium consumption in men and diabetes mellitus in women are the most important risk factors of premature coronary artery disease in Iran. *Int J Cardiol.* 2010; 141(1):116–8. [PubMed: 19346018]
13. Safaai N, Kazemi B. Effect of opium use on short-term outcome in patients undergoing coronary artery bypass surgery. *Gen Thorac Cardiovasc Surg.* 2010; 58(2):62–7. [PubMed: 20155341]
14. Masoomi M, Ramezani MA, Karimzadeh H. The relationship of opium addiction with coronary artery disease. *Int J Prev Med.* 2010; 1(3):182–6. [PubMed: 21566789]
15. Khademi H, Malekzadeh R, Pourshams A, et al. Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50,000 adults in Iran. *BMJ.* 2012; 344:e2502. [PubMed: 22511302]
16. Atici S, Cinel I, Cinel L, Doruk N, Eskandari G, Oral U. Liver and kidney toxicity in chronic use of opioids: an experimental long term treatment model. *J Biosci.* 2005; 30(2):245–52. [PubMed: 15886461]
17. Wood JD, Galligan JJ. Function of opioids in the enteric nervous system. *Neurogastroenterol Motil.* 2004; 16(Suppl 2):17–28. [PubMed: 15357848]
18. Hewer T, Rose E, Ghadirian P, et al. Ingested mutagens from opium and tobacco pyrolysis products and cancer of the oesophagus. *Lancet.* 1978; 2(8088):494–6. [PubMed: 79865]
19. Ribeiro Pinto LF, Swann PF. Opium and oesophageal cancer: effect of morphine and opium on the metabolism of N-nitrosodimethylamine and N-nitrosodiethylamine in the rat. *Carcinogenesis.* 1997; 18(2):365–9. [PubMed: 9054630]
20. Shakeri R, Malekzadeh R, Etemadi A, et al. Opium: An emerging risk factor for gastric adenocarcinoma. *Int J Cancer.* Published online first: 2013 Jan 15.
21. Sadjadi A, Derakhshan MH, Yazdanbod A, et al. Neglected role of hookah and opium in gastric carcinogenesis: A cohort study on risk factors and attributable fractions. *Int J Cancer.* Published online first: 2013 Jun 24.
22. Pourshams A, Saadatian-Elahi M, Nouraie M, et al. Golestan cohort study of oesophageal cancer: feasibility and first results. *Br J Cancer.* 2005; 92(1):176–81. [PubMed: 15597107]
23. Pourshams A, Khademi H, Malekshah AF, et al. Cohort Profile: The Golestan Cohort Study--a prospective study of oesophageal cancer in northern Iran. *Int J Epidemiol.* 2010; 39(1):52–9. [PubMed: 19332502]
24. Abnet CC, Saadatian-Elahi M, Pourshams A, et al. Reliability and validity of opiate use self-report in a population at high risk for esophageal cancer in Golestan, Iran. *Cancer Epidemiol Biomarkers Prev.* 2004; 13(6):1068–70. [PubMed: 15184266]
25. Khademi H, Etemadi A, Kamangar F, et al. Verbal autopsy: reliability and validity estimates for causes of death in the Golestan Cohort Study in Iran. *PLoS ONE.* 2010; 5(6):e11183. [PubMed: 20567597]
26. Ganji A, Malekzadeh F, Safavi M, et al. Digestive and Liver Disease Statistics in Iran. *Middle East Journal of Digestive Diseases.* 2009; 1(2):56–62.
27. Gao Y, Hu N, Han XY, et al. Risk factors for esophageal and gastric cancers in Shanxi Province, China: a case-control study. *Cancer epidemiol.* 2011; 35(6):e91–9. [PubMed: 21846596]
28. Kamangar F. Causality in epidemiology. *Arch Iran Med.* 2012; 15(10):641–7. [PubMed: 23020541]
29. Masood A. Opium smoking in the Frontier Province of Pakistan. *Bull Narc.* 1979; 31(1):59–66.
30. Sadeghi A, Behmard S, Vesselinovitch SD. Opium: a potential urinary bladder carcinogen in man. *Cancer.* 1979; 43(6):2315–21. [PubMed: 455221]
31. Malaveille C, Friesen M, Camus AM, et al. Mutagens produced by the pyrolysis of opium and its alkaloids as possible risk factors in cancer of the bladder and oesophagus. *Carcinogenesis.* 1982; 3(5):577–85. [PubMed: 7046981]
32. Shakeri R, Kamangar F, Nasrollahzadeh D, et al. Is opium a real risk factor for esophageal cancer or just a methodological artifact? Hospital and neighborhood controls in case-control studies. *PLoS ONE.* 2012; 7(3):e32711. [PubMed: 22396792]
33. Merat S, Rezvan H, Nouraie M, et al. The prevalence of hepatitis B surface antigen and anti-hepatitis B core antibody in Iran: a population-based study. *Arch Iran Med.* 2009; 12(3):225–31. [PubMed: 19400598]

34. Angulo P. Nonalcoholic fatty liver disease. *New Engl J Med*. 2002; 346(16):1221–31. [PubMed: 11961152]
35. Friesen M, O'Neill IK, Malaveille C, et al. Substituted hydroxyphenanthrenes in opium pyrolysates implicated in oesophageal cancer in Iran: structures and in vitro metabolic activation of a novel class of mutagens. *Carcinogenesis*. 1987; 8(10):1423–32. [PubMed: 3652380]
36. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. IARC monographs on the evaluation of carcinogenic risks to humans. Ingested nitrate and nitrite, and cyanobacterial peptide toxins. *IARC Monogr Eval Carcinog Risks Hum*. 2010; 94:v–vii. 1–412. [PubMed: 21141240]
37. Shakeri R, Malekzadeh R, Etemadi A, et al. Opium: An emerging risk factor for gastric adenocarcinoma. *Int J Cancer*. 2013
38. Pacifici GM, Bencini C, Rane A. Presystemic glucuronidation of morphine in humans and rhesus monkeys: subcellular distribution of the UDP-glucuronyltransferase in the liver and intestine. *Xenobiotica*. 1986; 16(2):123–8. [PubMed: 3083607]
39. van der Laan JW, Krajnc EI, Krajnc-Franken MA, et al. Immunotoxicological screening of morphine and methadone in an extended 28 day study in rats. *Int J Immunopharmacol*. 1995; 17(6):535–43. [PubMed: 7499032]
40. Sumathi T, Niranjali Devaraj S. Effect of *Bacopa monniera* on liver and kidney toxicity in chronic use of opioids. *Phytomed*. 2009; 16(10):897–903.
41. Borzelleca JF, Egle JJ, Harris LS, et al. Toxicological evaluation of mu-agonists. Part I: Assessment of toxicity following 30 days of repeated oral dosing of male and female rats with levo-alpha-acetylmethadol HCl (LAAM). *J Appl Toxicol*. 1994; 14(6):435–46. [PubMed: 7884149]
42. Nagamatsu K, Ohno Y, Ikebuchi H, et al. Morphine metabolism in isolated rat hepatocytes and its implications for hepatotoxicity. *Biochem pharmacol*. 1986; 35(20):3543–8. [PubMed: 2429666]
43. Bekheet SH. Morphine sulphate induced histopathological and histochemical changes in the rat liver. *Tissue Cell*. 2010; 42(4):266–72. [PubMed: 20655561]
44. Abu-Shanab A, Quigley EM. The role of the gut microbiota in nonalcoholic fatty liver disease. *Nat Rev Gastroenterol Hepatol*. 2010; 7(12):691–701. [PubMed: 21045794]
45. DuPont AW, DuPont HL. The intestinal microbiota and chronic disorders of the gut. *Nat Rev Gastroenterol Hepatol*. 2011; 8(9):523–31. [PubMed: 21844910]
46. Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature*. 2011; 472(7341):57–63. Epub 2011/04/09. [PubMed: 21475195]
47. Maloy KJ, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. *Nature*. 2011; 474(7351):298–306. Epub 2011/06/17. [PubMed: 21677746]
48. Bosshart H. Morphine and cancer progression: hydrogen peroxide points to need for more research. *J Opioid manag*. 2011; 7(2):93–6. [PubMed: 21561032]
49. Mousavi MR, Damghani MA, Haghdoust AA, Khamesipour A. Opium and risk of laryngeal cancer. *Laryngoscope*. 2003; 113(11):1939–43. [PubMed: 14603052]
50. Fimiani C, Arcuri E, Santoni A, et al. Mu3 opiate receptor expression in lung and lung carcinoma: ligand binding and coupling to nitric oxide release. *Cancer Lett*. 1999; 146(1):45–51. [PubMed: 10656608]
51. Behmard S, Sadeghi A, Mohareri MR, et al. Positive association of opium addiction and cancer of the bladder. Results of urine cytology in 3,500 opium addicts. *Acta Cytol*. 1981; 25(2):142–6. [PubMed: 6941612]
52. Da Costa JL, Tock EP, Boey HK. Lung disease with chronic obstruction in opium smokers in Singapore. Clinical, electrocardiographic, radiological, functional and pathological features. *Thorax*. 1971; 26(5):555–71. [PubMed: 5134057]
53. Ghodse AH, Myles JS. Asthma in opiate addicts. *J Psychosom Res*. 1987; 31(1):41–4. [PubMed: 3820144]
54. Agius R. Opiate inhalation and occupational asthma. *BMJ*. 1989; 298(6669):323.
55. Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of analgesics in older adults with arthritis. *Archives of internal medicine*. 2010; 170(22):1968–76. [PubMed: 21149752]

56. Gomes T, Mamdani MM, Dhalla IA, et al. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*. 2011; 171(7):686–91. [PubMed: 21482846]
57. Dhalla IA, Mamdani MM, Sivilotti ML, et al. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ*. 2009; 181(12):891–6. [PubMed: 19969578]
58. Fischer B, Rehm J. Deaths related to the use of prescription opioids. *CMAJ*. 2009; 181(12):881–2. [PubMed: 19969577]
59. Dhalla IA. Opium, opioids, and an increased risk of death. *BMJ*. 2012; 344:e2617. [PubMed: 22511303]
60. Degenhardt L, Randall D, Hall W, et al. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend*. 2009; 105(1–2):9–15. [PubMed: 19608355]
61. Roohafza H, Talaei M, Sadeghi M, et al. Opium decreases the age at myocardial infarction and sudden cardiac death: a long- and short-term outcome evaluation. *Arch Iran Med*. 2013; 16(3): 154–60. [PubMed: 23432167]
62. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med*. 2010; 363(21):1981–5. [PubMed: 21083382]
63. Reece AS. Commentary on Opium Use and Mortality in Golestan Cohort Study. *Arch Iran Med*. 2012; 15:588–90.
64. Darke S, Duflou J, Torok M. The comparative toxicology and major organ pathology of fatal methadone and heroin toxicity cases. *Drug Alcohol Depend*. 2010; 106(1):1–6. [PubMed: 19720472]
65. Reece AS. Differing age related trajectories of dysfunction in several organ systems in opiate dependence. *Aging Clin Exp Res*. 2012; 24(1):85–96. [PubMed: 21339699]
66. Reece AS, Davidson P. Deficit of circulating stem--progenitor cells in opiate addiction: a pilot study. *Substance abuse treatment, prevention, and policy*. 2007; 2:19.

Study highlights

1. WHAT IS CURRENT KNOWLEDGE

- There is evidence from physiologic and animal studies that long-term use of opiates may affect the gastrointestinal tract in adverse ways.
- A number of retrospective epidemiologic studies have suggested long-term opium consumption is a risk factor for development of upper gastrointestinal cancers.
- A recent report from a prospective cohort study showed that long-term low-dose opium use was associated with a doubling of all-cause mortality.

2. WHAT IS NEW HERE

- This is the first prospective study that has focused on the association between opium use and malignant and nonmalignant digestive disease-related mortality.
- After adjustment for confounders, opium use was associated with a 55% increased risk of all-cause GI mortality.
- Our results showed a strong association between opium use and death from liver cirrhosis, even after adjustment for HBV infection.

Figure 1.

The GCS flowchart of enrollment, and the outcome events through 17 December 2012 (*).

Table 1

Descriptive characteristics of the cohort participants, and associations with mortality due to gastrointestinal causes of death

	Number of cohort participants	Total GI deaths (SMR)*	RR (95%CI) [#] for all GI mortality	Malignant GI deaths (SMR)*	RR (95%CI) [#] for malignant GI mortality	Non-malignant GI deaths (SMR)*	RR (95%CI) [#] for non-malignant GI mortality
Gender							
Female	28,811	189 (105)	ref	151 (85)	ref	38 (20)	ref
Male	21,234	285 (201)	1.9 (1.5 – 2.5)	236 (166)	2.0 (1.5 – 2.6)	49 (35)	1.8 (1.0 – 3.2)
Residential Place							
Rural	40,012	384 (163)	ref	323 (139)	ref	61 (24)	ref
Urban	10,033	90 (111)	0.7 (0.5 – 0.9)	64 (78)	0.6 (0.4 – 0.8)	26 (33)	1.4 (0.8 – 2.4)
Ethnicity							
Non-Turkmen	12,792	94 (107)	ref	71 (78)	ref	23 (29)	ref
Turkmen	37,253	380 (166)	1.6 (1.2 – 2.0)	316 (142)	1.8 (1.4 – 2.4)	64 (25)	0.9 (0.5 – 1.5)
Marital status							
Married	43,890	370 (150)	ref	305 (124)	ref	65 (25)	ref
Single	302	1 (86)	0.6 (0.4 – 0.8)	1 (86)	0.7 (0.5 – 0.9)	0 (0)	-
Widow/er	5,603	101 (173)	1.2 (0.9 – 1.5)	79 (131)	1.1 (0.8 – 1.4)	22 (42)	1.7 (0.9 – 2.9)
Divorced	220	2 (135)	0.9 (0.7 – 1.4)	2 (135)	1.1 (0.9 – 1.4)	0 (0)	-
Education							
Illiterate	35,118	385 (152)	ref	318 (128)	ref	67 (25)	ref
Up to 8 years	10,708	62 (122)	0.8 (0.6 – 1.0)	51 (99)	0.8 (0.6 – 1.0)	11 (24)	1.0 (0.5 – 1.8)
High-school	3,155	18 (139)	0.9 (0.7 – 1.2)	11 (91)	0.7 (0.5 – 0.9)	7 (48)	1.9 (1.2 – 3.3)
University degree	1,064	9 (332)	2.2 (1.8 – 2.7)	7 (181)	1.4 (1.1 – 1.8)	2 (151)	6.0 (3.9 – 9.6)
Alcohol consumption							
Never use	48,316	456 (149)	ref	377 (125)	ref	79 (25)	ref
Ever use	1,729	18 (166)	1.1 (0.9 – 1.4)	10 (82)	0.7 (0.5 – 0.9)	8 (83)	3.3 (2.1 – 5.4)
Cigarette smoking							
Never smokers	41,382	333 (125)	ref	273 (20)	ref	60 (21)	ref
Ever smokers	8,663	141 (264)	2.1 (1.7 – 2.6)	114 (59)	3.0 (1.8 – 5.2)	27 (51)	2.4 (1.4 – 4.3)
Opium use							
Never users	41,558	330 (127)	ref	276 (107)	ref	54 (20)	ref

	Number of cohort participants	Total GI deaths (SMR) [*]	RR (95%CI) [#] for all GI mortality	Malignant GI deaths (SMR) [*]	RR (95%CI) [#] for malignant GI mortality	Non-malignant GI deaths (SMR) [*]	RR (95%CI) [#] for non-malignant GI mortality
Ever users	8,487	144 (255)	2.0 (1.6 – 2.5)	111 (196)	1.8 (1.4 – 2.3)	33 (59)	3.0 (1.8 – 5.2)

^{*} SMR: Age standardized mortality rate in the GCS in 10⁵ person-years by World population 2000.

[#]RR: Relative Risk of mortality, adjusted for age. Relative risks were obtained by dividing the SMRs.

Table 2

Hazard ratios for the association between opium use and gastrointestinal mortality by type of opiate used, route of administration, and cumulative use

	All GI mortality			Malignant GI mortality			Non-malignant GI mortality		
	No. of participants (deaths)	Cox HR (95%CI) *	No. of participants (deaths)	Cox HR (95%CI) *	No. of participants (deaths)	Cox HR (95%CI) *	No. of participants (deaths)	Cox HR (95%CI) *	
Opium Use									
Never users	41,558 (330)	ref	41,558 (276)	ref	41,558 (54)	ref	41,558 (54)	ref	
Ever Users	8,487 (144)	1.55 (1.24 – 1.93)	8,487 (111)	1.38 (1.07 – 1.76)	8,487 (33)	2.60 (1.57 – 4.31)			
Opium cumulative use (nokhod-days)									
Never users	41,558 (330)	ref	41,558 (276)	ref	41,558 (54)	ref	41,558 (54)	ref	
Former users	868 (14)	1.22 (0.71 – 2.12)	868 (10)	1.01 (0.53 – 1.93)	868 (4)	2.55 (0.88 – 7.40)	868 (4)	2.55 (0.88 – 7.40)	
1st fifth (<1200)	1,524 (19)	1.34 (0.84 – 2.14)	1,524 (13)	1.08 (0.62 – 1.90)	1,524 (6)	2.79 (1.17 – 6.63)	1,524 (6)	2.79 (1.17 – 6.63)	
2nd fifth (1201–4696)	1,524 (22)	1.49 (0.96 – 2.31)	1,524 (17)	1.33 (0.81 – 2.19)	1,524 (5)	2.44 (0.95 – 6.26)	1,524 (5)	2.44 (0.95 – 6.26)	
3rd fifth (4697–12418)	1,524 (22)	1.41 (0.91 – 2.20)	1,524 (17)	1.25 (0.76 – 2.06)	1,524 (5)	2.42 (0.94 – 6.24)	1,524 (5)	2.42 (0.94 – 6.24)	
4th fifth (12419–30681)	1,570 (24)	1.47 (0.96 – 2.25)	1,570 (19)	1.35 (0.83 – 2.17)	1,570 (5)	2.16 (0.83 – 5.63)	1,570 (5)	2.16 (0.83 – 5.63)	
5th fifth (>30681)	1,477 (43)	2.21 (1.57 – 3.13)	1,477 (35)	2.04 (1.39 – 2.99)	1,477 (8)	3.29 (1.45 – 7.45)	1,477 (8)	3.29 (1.45 – 7.45)	
<i>p for trend = 0.037</i>									
<i>p for trend = 0.030</i>									
<i>p for trend = 0.73</i>									
Routes of administration									
Never users	41,558 (330)	ref	41,558 (276)	ref	41,558 (54)	ref	41,558 (54)	ref	
Smoking	5,804 (76)	1.38 (1.05 – 1.81)	5,804 (61)	1.30 (0.96 – 1.75)	5,804 (15)	1.86 (1.00 – 3.48)	5,804 (15)	1.86 (1.00 – 3.48)	
Ingestion	2,176 (57)	1.83 (1.35 – 2.47)	2,176 (42)	1.50 (1.06 – 2.13)	2,176 (15)	4.07 (2.15 – 7.71)	2,176 (15)	4.07 (2.15 – 7.71)	
Both methods	497 (11)	1.73 (0.93 – 3.20)	497 (8)	1.42 (0.69 – 2.91)	497 (3)	3.75 (1.12 – 12.6)	497 (3)	3.75 (1.12 – 12.6)	
Opium Types									
Never users	41,558 (330)	ref	41,558 (276)	ref	41,558 (54)	ref	41,558 (54)	ref	
Teriak only	7,308 (125)	1.55 (1.23 – 1.94)	7,308 (99)	1.41 (1.09 – 1.81)	7,308 (26)	2.38 (1.40 – 4.04)	7,308 (26)	2.38 (1.40 – 4.04)	
Shireh only	781 (14)	1.79 (1.03 – 3.09)	781 (8)	1.19 (0.58 – 2.43)	781 (6)	5.45 (2.23 – 13.3)	781 (6)	5.45 (2.23 – 13.3)	
Sukhteh only	6 (0)	-	6 (0)	-	6 (0)	-	6 (0)	-	
Heroin only	4 (0)	-	4 (0)	-	4 (0)	-	4 (0)	-	
Combinations	388 (5)	1.16 (0.47 – 2.83)	388 (4)	1.06 (0.39 – 2.89)	388 (1)	1.74 (0.23 – 13.1)	388 (1)	1.74 (0.23 – 13.1)	

* Results are obtained from Cox regression models with age as the time scale. The models were further adjusted for sex, residential place, ethnicity, cigarette smoking, alcohol consumption, and HBV infection

Table 3

Results for major causes of digestive disease death associated with opium use, and sensitivity analyses

GI Mortality	Cox HR* for opium use, compared to never users		
	in all participants	after excluding deaths occurring during the first 12 months after enrollment	after excluding participants who started opium use after experiencing a major chronic disease**
All (n = 474)	1.55 (1.24 – 1.93)	1.44 (1.14 – 1.83)	1.60 (1.28 – 2.01)
Malignant (n = 387)	1.38 (1.07 – 1.76)	1.31 (1.01 – 1.70)	1.43 (1.11 – 1.84)
Esophageal cancer (n = 134)	1.55 (1.02 – 2.34)	1.54 (0.99 – 2.38)	1.69 (1.11 – 2.56)
Gastric Cancer (n = 125)	1.19 (0.78 – 1.83)	1.19 (0.76 – 1.84)	1.22 (0.79 – 1.89)
Other (n = 128)	1.39 (0.90 – 2.16)	1.21 (0.74 – 1.96)	1.40 (0.89 – 2.21)
Non-malignant (n = 87)	2.60 (1.57 – 4.31)	2.23 (1.29 – 3.88)	2.63 (1.57 – 4.42)
Cirrhosis (n = 37)	2.29 (1.04 – 5.07)	2.07 (0.91 – 4.70)	2.05 (0.88 – 4.77)
Other (n = 50)	2.86 (1.49 – 5.50)	2.38 (1.13 – 5.00)	3.10 (1.60 – 6.00)

* Results are obtained from Cox regression models with age as the time scale. The models were further adjusted for sex, residential place, ethnicity, cigarette smoking, alcohol consumption, and HBV infection

** Major chronic diseases included coronary heart disease, cerebrovascular accidents, diabetes melitus, and hypertension