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Opium Use and Risk of Pancreatic Cancer: A Prospective Cohort Study

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Abstract

Background—We examined the association between opium consumption and pancreatic cancer incidence in a large-scale prospective cohort of the general population in Northeast of Iran.

Methods—A total of 50,045 adults were systematically followed-up (median of 7.4 years) and incident cases of pancreatic cancer were identified. Self-reported data on opium consumption was collected at baseline. Cumulative use (-year) was defined as number of nokhods (a local unit, approximately 0.2 g) of opium consumed per day multiplied by number of years consuming. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between

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opium consumption and pancreatic cancer were calculated using Cox proportional hazards regression models.

Results—Overall, 54 confirmed cases of pancreatic cancer were identified. Opium use of more than 81 nokhod-years (high cumulative use), compared to never use, was strongly associated with pancreatic cancer even after adjustments for multiple potential confounding factors [HR=3.01; 95% CI 1.25-7.26]. High cumulative consumption of opium was significantly associated with risk of pancreatic cancer after adjusting for cumulative dose of cigarette smoking [HR=3.56; 95% CI 1.49-8.50]. In a sensitivity analysis, we excluded participants (including 2 pancreatic cancer cases) who were recruited within the first 5 years of starting opium consumption; high cumulative use of opium was still associated with pancreatic cancer risk [HR=2.75; 95% CI 1.14-6.64].

Conclusion—Our results showed a positive association between opium consumption and pancreatic cancer.

Impact—This is the first prospective large-scale study to show the association of opium consumption with pancreatic cancer as a risk factor.

Keywords

opium; pancreatic cancer; risk

Introduction

Pancreatic cancer is the seventh cause of cancer mortality in men and women worldwide (1) and the seventh most common cancer diagnosed in the Golestan Cohort Study (GCS) in Northeast of Iran (2). Several potentially modifiable risk factors have been proposed for pancreatic cancer (3), including high body mass index (BMI) (4, 5) and diabetes mellitus (DM) (6), while smoking is the strongest identified environmental risk factor of pancreatic cancer (3). Smokeless and other non-tobacco cigarettes also pose a risk to pancreatic cancer (7). Little is known about the role of opium consumption in pancreatic cancer development.

Opium is a commonly used substance for recreational and medical purposes in some parts of the world. Opium is the most commonly abused drug in Iran with an estimated 20% of the adult population consuming (8). It is either smoked or ingested. There is great interest in identifying the role of opium consumption as a risk factor of diseases including gastrointestinal cancers (9). Opium use was associated with increased mortality of all causes and gastrointestinal cancer deaths in a prospective cohort study in Northern Iran (10, 11). Several other studies have also shown a positive association between opium consumption and higher risk of cancers of the esophagus (12), stomach (13, 14), bladder (15), larynx (16), and lung (17). Previous reports have identified several mutagenic compounds in opium and its pyrolysed derivatives (18–20). It is not known if opium causes cancer directly through mutagenic compounds that are generated during pyrolysis of opium, or indirectly through the effect of its alkaloids (e.g. morphine) on the peristalsis of the intestinal tract (21, 22). We recently observed a higher risk of pancreatic cancer for opium ever users in a case-control study (23). Therefore, our objective was to further investigate our preliminary results on the association of opium consumption as a risk factor with pancreatic cancer incidence in a population-based prospective cohort.

Materials and Methods

Study population

A total of 50,045 adults [21,241 (42.4%) men] were recruited in the GCS from urban and rural areas of Golestan Province, Northeast of Iran between January 2004 and June 2008 (2). The main objective of GCS was to identify risk factors of oesophageal cancer, which has a high incidence rate in Golestan. Baseline collected data included but were not limited to ethnicity, occupational history, past medical history, family history of cancer, cigarette smoking, and opium and alcohol consumption. DM at baseline was either self-reported or determined by the trained staff based on the use of antigyclemic medications. Anthropometric indices were measured by trained staff. Cigarette smoking ever or current use and the number used per day were self-reported. The Institutional Review Board of the Digestive Disease Research institute, the US National Cancer Institute, and the International Agency for Research on Cancer approved the study. Written informed consent was obtained from all participants at enrollment.

Opium consumption data

Opium consumption was self-reported in 17% of the cohort participants. High level of accuracy of self-reported opium consumption had been previously verified in a subgroup of cohort participants by means of measuring opioid metabolites in the urine samples (24). Data were collected on the amount of use in local unit (nokhod, approximately 0.2 g); duration and frequency of consumption; and routes of administration (10). Data were collected separately in case of consumption of different opium types or intermittent consumption. Cumulative use (nokhod-year) was defined as number of nokhods of opium consumed per day multiplied by number of years consuming. The cumulative use was employed to test the dose-response relationships as previously described (11).

Pancreatic cancer ascertainment

The GCS participants were systematically followed-up and incidents of hospitalisation and major diseases including pancreatic cancer were registered in central databases of Golestan Cancer Registry. Upon reporting of endoscopy, cancer, or death, the case was further investigated to collect all available clinical, laboratory, and pathology reports. In addition, a validated verbal autopsy questionnaire was administered to the closest relative of the deceased participants (2). Two internists separately reviewed the documents to ascertain the cause of death. Any discordance was resolved by a third senior internist (10, 25). Designated pancreatic cancer cases were re-ascertained by a senior gastroenterologist (MM) based on reported clinical signs and symptoms, imaging findings, histopathology report, and clinical follow up. The success rate for follow-up was 99%.

Statistical analysis

Continuous and categorical variables were compared by Oneway ANOVA and Chi Square, respectively. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between opium consumption and pancreatic cancer were calculated using Cox proportional hazards regression models controlling for other pancreatic cancer risk factors

i.e. age (continuous), sex, BMI (continuous), DM, and cigarette smoking. The effect of cigarette smoking was controlled for ever *vs.* never use, former *vs.* current use, and the cumulative dose (total pack/year) in separate models. The proportional hazard assumption was verified using Schoenfeld residuals. Duration of follow up until loss to follow-up, death, or 1 June 2015 (whichever came first) was considered as the timescale. Multiplicative interactions between cigarette smoking (ever use) and opium consumption (ever use and cumulative dose) were assessed using likelihood ratio test. Sensitivity analysis was conducted after excluding participants who were recruited within the first 5 years of starting opium consumption. A P value of less than 0.05 was considered significant. Statistical analyses were performed using STATA (version 12; StataCorp, College Station, TX, USA).

Results

During a median follow-up of 7.4 years (353,920 person-years), 54 cases of pancreatic cancer were identified in GCS. The mean age (standard deviation) of cohort participants and pancreatic cancer patients at enrolment was 52.1 (8.9) and 58.5 (9.0) years, respectively. At baseline, eventual pancreatic cancer cases were older ($p<0.001$) and more likely to be a cigarette smoker ($p=0.002$) and have a lower BMI ($p=0.022$) than others. Ever opium use was reported by 8483 cohort participants (17.0%) and 17 pancreatic cancer patients (31.5%) (p for difference=0.005) (Table S1). In total, 1727 (3.5%) of the participants consumed ≥81 nokhod-year (≥ 5th quintile) opium. Participants with high cumulative opium consumption were predominantly male ($p<0.001$) and reported significantly higher cigarette smoking and alcohol consumption (Table 1). High cumulative opium consumption was detected in 8 (14.8%) of pancreatic cancer patients and 1719 (3.4%) of the rest of the cohort. Characteristics of participants based on opium consumption are summarized in Table 1.

Routes of administration of opium included inhalation (9, 53%), ingestion (6, 35%), and both (2, 12%) in pancreatic cancer patients. We did not detect a significant difference between different routes of opium administration and the risk of pancreatic cancer. Nevertheless, we detected a larger effect of opium ingestion on the risk of pancreatic cancer [HR=2.38; 95% CI 1.00-5.69, p=0.05] than inhalation [HR=1.88; 95% CI 0.91-3.89, p=0.090] in univariate analysis.

Opium ever use was not significantly associated with increased pancreatic cancer risk when adjusted for confounding factors including age, sex, cigarette smoking (never, Former, or current use), alcohol consumption, BMI, and DM (HR=1.47; 95% CI 0.75-2.88). However, opium cumulative use of more than 81 nokhod-year was significantly associated with increased risk of pancreatic cancer in multivariate analysis [HR=2.92; 95% CI 1.20-7.12] (Table 2). In a sensitivity analysis, we excluded participants who were recruited within the first 5 years of starting opium consumption (n=2053 including 2 cases of pancreatic cancer). High dose of opium consumption was still significantly associated with pancreatic cancer risk compared to never use [HR=2.93; 95% CI 1.21-7.07, p=0.017]. Moreover, high dose opium consumption was significantly associated with pancreatic cancer risk when adjusted for other aspects of cigarette smoking including current use [HR=3.44; 95% (1.47-8.07)] and cumulative dose [HR=3.56; 95% 1.49-8.50] (Table S2).

Cigarette smoking is a known risk factor of pancreatic cancer (26). We also observed a significantly higher number of cigarette smokers in pancreatic cancer patients in comparison to the rest of the cohort (33.3% *vs.* 17.3%, p=0.002). There is a positive association between ever cigarette smoking and cumulative dose with higher risk of pancreatic cancer in multivariate analysis adjusted for age, sex, alcohol consumption, BMI and DM [HR=2.25; 95% CI 1.11-4.57] and [HR=1.01; 95% CI 1.00-1.01], respectively. However, after controlling for the dose of opium consumption, the relationship between cigarette smoking and the risk of pancreatic cancer was not statistically significant [HR=1.85; 95%CI 0.87-3.97] for ever use and [HR=1.01; 95% CI 0.99-1.02] for cumulative dose. The interactions between cigarette smoking (ever use) and opium consumption (ever use or cumulative dose) were not statistically significant (p=0.544 and 0.886, respectively). Of the participants who reported low and high dose opium consumption, 3,298 (48.7%) and 1,188 (68.8%) reported ever cigarette smoking, respectively (Table 1). Next, we aimed to examine the modifying effect of cigarette smoking on opium consumption as a risk factor of pancreatic cancer. Overall, 74.7% and 57.4% of cohort participants and participants who later developed pancreatic cancer did not consume opium and did not smoke cigarette, respectively. We modeled joint categories of opium consumption (never, < 81, and ≥ 81) by smoking (never and ever) in two models of multivariate analyses where one was adjusted for age, sex, alcohol consumption, DM, and BMI and the other was further adjusted for cigarette smoking cumulative dose. Cigarette smoking in the absence of opium consumption is associated with increased risk of pancreatic cancer, albeit not significantly [HR=1.69; 95% CI 0.64-4.51]. In contrast, low dose opium consumption in the absence of cigarette smoking was insufficient to confer a significantly higher risk of pancreatic cancer [HR=0.92; 95% CI 0.28-3.04]. High dose opium use in non-smokers or low dose opium use in smokers were associated with increased risk of pancreatic cancer but did not reach statistical significance. However, concomitant cigarette smoking and high dose opium consumption resulted in increased risk of pancreatic cancer in our population [HR=5.38; 95% CI 1.96-14.75]. Similar observation was made after further adjustment for cigarette smoking cumulative dose [HR=5.78; 95% CI 1.85-18.05] (Table 3).

Discussion

This is the first prospective cohort study observing that opium consumption is associated with an increased risk of pancreatic cancer in a dose dependent manner. Unlike cigarette smoking, opium consumption has been less studied as a potentially cancer-predisposing risk factor. We detected that a significantly higher proportion of patients with pancreatic cancer reported ever use of opium. Those who used higher cumulative doses of opium (≥5th quintile) demonstrated a 4 times higher risk of pancreatic cancer. This still existed after adjustments for multiple potentially confounding factors, including age, sex, cigarette smoking, alcohol consumption, BMI, and DM. Based on results of this study and several other studies of opium use and cancer, opium is now suggested to be an emerging cancer risk factor (9).

In 353,920 person-years of follow-up, we identified 54 pancreatic cancer mortalities, yielding a crude mortality rate of about 13.5 in 100,000 person-years (equivalent to 19.3 in 100,000 person-years age-standardized mortality rate according to WHO world population

in 2015). According to Golestan Cancer Registry, the mortality rates of pancreatic cancer in the general population are 0.8 and 0.3 in 100,000 person-year in men and women, respectively (personal communication). It should be noted that the ages of the GCS participants were 45 years and older and thus, higher rates of cancers (including pancreatic cancer) is not surprising. Indeed, it is in line with the available country-specific statistics on death due to pancreatic cancer at the Institute for Health Metrics and Evaluation (http://vizhub.healthdata.org/cod/ access date: 1 May 2016).

Opium and its derivatives may be used to alleviate pain from cancer (27). To address the reverse causality between opium consumption and pancreatic cancer; we performed a sensitivity analysis excluding participants who consumed opium less than 5 years at the time of recruitment. High cumulative opium consumption was still significantly associated with pancreatic cancer implying that the effect is not due to the reverse causality.

Opium is considered as a genotoxic substance (28). Previous reports have identified several mutagenic compounds in opium and its pyrolysed derivatives (18–20). Opioid mutagenic compounds can reach the pancreas (3) and may initiate a tumourigenesis process. In addition to the mutagenic property of opium derivatives, it is shown that opium can have biologic effects on various aspects of tumourigenesis process, including proliferation, apoptosis, and angiogenesis. For example, it has been shown that opium can induce angiogenesis and increase breast cancer growth rate in mouse models (29). In fact, opium antagonists have been tested for their anti-tumour capacity (30). Recent evidence suggests that opiates have a possible direct effect on lung cancer growth, progression, and epithelial-mesenchymal transition via μ opioid receptor (31–33). Similar effect was also observed in hepatocellular carcinoma (34). In accordance, μ-opioid receptor gene (OPRM1) polymorphism has been associated with breast cancer (35) and breast cancer survival (36). Opioid receptors are also present in human pancreas (37); therefore, it is conceivable that activation of pancreas opioid receptor could affect the proliferation capacity of the tumourigenic cells and as such facilitate tumor promotion.

For the first time, we observed that opium consumption might modify the association of cigarette smoking with pancreatic cancer, although multiplicative interaction was not detected. Although, cigarette smoking is associated with higher risk of pancreatic cancer in our population; further controlling for opium consumption, we found that cigarette smoking or opium consumption alone were not statistically significantly associated with higher risk of pancreatic cancer which is in accordance with our previous case-control study (23). However, high dose opium use was associated with pancreatic cancer when we tightly controlled for cigarette smoking. Indeed, examining the effect of concomitant cigarette smoking and opium consumption revealed that the combined cigarette smoking and high dose opium use has a high HR of 5.4 for pancreatic cancer which is nearly 1.7 times the HR of high dose opium use in nonsmokers and 1.5 times the HR of ever opium users. Former smokers' risk of pancreatic cancer is negatively associated with the duration since the last use, reaching the level of non-smokers after five years of quitting (38, 39). However, the time of quitting is not available in our cohort and thus we were unable to assess the impact of the duration of not smoking in former smokers in relation to the effect of opium consumption on pancreatic cancer. In our study, opium consumption is not associated with

an increased risk of pancreatic cancer in non-smokers. Likewise, it is plausible that opium consumption would not be associated with altered risk of pancreatic cancer in former smokers who quit more than five years. Moreover, although, we observed an interaction between cigarette smoking and opium consumption in pancreatic cancer, small number of cases and unavailability of data on the duration of quitting in former smokers are limiting factors in comparing the strength of association of cigarette smoking and opium consumption in the risk of pancreatic cancer.

Inorganic Lead is considered a probable carcinogen to humans (40) and is associated with increased risk of many cancer types including pancreatic cancer (41, 42). It is argued that opium in Iran could be contaminated with lead and hence, its carcinogenic effect may be over-estimated (43). Indeed, opium consumers had higher blood lead levels in a separate study conducted in Iran (44). Although, we have not assessed the lead contamination of the opium used in the Golestan region, it is highly unlikely that chronic lead toxicity remains asymptomatic. Although, high BMI (4, 5) and DM (6) are known risk factors of pancreatic cancer, we observed that our pancreatic cancer patients had a slightly lower BMI and lower prevalence of DM compared to the rest of the cohort. This could potentially be explained by reverse causation given the short period between start of the follow-up and diagnosis of pancreatic cancer. In addition, we cannot exclude the possibility of residual confounding by DM as well as cigarette smoking mainly due to reliance on self-reporting specifically for DM. The overall small number of pancreatic cancer cases limits the power of our study. Nevertheless, this study's strengths are its population-based, prospective design and collection of data using a validated questionnaire.

In conclusion, our results showed a positive association between opium consumption and risk of pancreatic cancer. This association was dose-dependent and contingent on the cigarette smoking, although multiplicative interaction could not be detected. Nonetheless, caution is warranted due to the small number of cases in our study. Moreover, epidemiological studies should be followed by molecular investigations to elucidate the potential mechanism(s) of action.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations list

BMI	body mass index
CI	Confidence interval

DM	diabetes mellitus
GCS	Golestan Cohort Study
HR	hazard ratios
OPRM1	μ-opioid receptor gene

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015; 65:87–108. [PubMed: 25651787]
2. Pourshams A, Khademi H, Malekshah AF, Islami F, Nouraei M, Sadjadi AR, et al. Cohort Profile: The Golestan Cohort Study–a prospective study of oesophageal cancer in northern Iran. Int J Epidemiol. 2010; 39:52–9. [PubMed: 19332502]
3. Lowenfels AB, Maisonneuve P. Epidemiology and prevention of pancreatic cancer. Jpn J Clin Oncol. 2004; 34:238–44. [PubMed: 15231857]
4. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. Int J Cancer. 2007; 120:1993–8. [PubMed: 17266034]
5. Arslan AA, Helzlsouer KJ, Kooperberg C, Shu XO, Steplowski E, Bueno-de-Mesquita HB, et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Arch Intern Med. 2010; 170:791–802. [PubMed: 20458087]
6. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer. 2005; 92:2076–83. [PubMed: 15886696]
7. Alguacil J, Silverman DT. Smokeless and other noncigarette tobacco use and pancreatic cancer: a case-control study based on direct interviews. Cancer Epidemiol Biomarkers Prev. 2004; 13:55–8. [PubMed: 14744733]
8. Zarghami M. Iranian Common Attitude Toward Opium Consumption. Iran J Psychiatry Behav Sci. 2015; 9:e2074. [PubMed: 26288642]
9. Kamangar F, Shakeri R, Malekzadeh R, Islami F. Opium use: an emerging risk factor for cancer? Lancet Oncol. 2014; 15:e69–77. [PubMed: 24480557]
10. Khademi H, Malekzadeh R, Pourshams A, Jafari E, Salahi R, Semnani S, 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]
11. Malekzadeh MM, Khademi H, Pourshams A, Etemadi A, Poustchi H, Bagheri M, et al. Opium use and risk of mortality from digestive diseases: a prospective cohort study. Am J Gastroenterol. 2013; 108:1757–65. [PubMed: 24145676]
12. Nasrollahzadeh D, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet CC, et al. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. Br J Cancer. 2008; 98:1857–63. [PubMed: 18475303]
13. Shakeri R, Malekzadeh R, Etemadi A, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, et al. Opium: an emerging risk factor for gastric adenocarcinoma. Int J Cancer Journal. 2013; 133:455–61.
14. Sadjadi A, Derakhshan MH, Yazdanbod A, Boreiri M, Parsaeian M, Babaei M, et al. Neglected role of hookah and opium in gastric carcinogenesis: a cohort study on risk factors and attributable fractions. Int J Cancer. 2014; 134:181–8. [PubMed: 23797606]
15. Hosseini SY, Safarinejad MR, Amini E, Hooshyar H. Opium consumption and risk of bladder cancer: A case-control analysis. Urol Oncol. 2010; 28:610–6. [PubMed: 19110453]
16. Mousavi MR, Damghani MA, Haghdoust AA, Khamesipour A. Opium and risk of laryngeal cancer. Laryngoscope. 2003; 113:1939–43. [PubMed: 14603052]
17. Masjedi MR, Naghan PA, Taslimi S, Yousefifard M, Ebrahimi SM, Khosravi A, et al. Opium could be considered an independent risk factor for lung cancer: a case-control study. Respiration. 2013; 85:112–8. [PubMed: 22759984]

18. Hewer T, Rose E, Ghadirian P, Castegnaro M, Malaveille C, Bartsch H, et al. Ingested mutagens from opium and tobacco pyrolysis products and cancer of the oesophagus. Lancet. 1978; 2:494–6. [PubMed: 79865]
19. Malaveille C, Friesen M, Camus AM, Garren L, Hautefeuille A, Bereziat JC, 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; 3:577–85. [PubMed: 7046981]
20. Friesen M, O'Neill IK, Malaveille C, Garren L, Hautefeuille A, Cabral JR, et al. Characterization and identification of 6 mutagens in opium pyrolysates implicated in oesophageal cancer in Iran. Mutat res. 1985; 150:177–91. [PubMed: 4000158]
21. Dowlatshahi K, Miller RJ. Role of opium in esophageal cancer: a hypothesis. Cancer research. 1985; 45:1906–7. [PubMed: 3978650]
22. Dowlatshahi K, Evander A, Walther B, Skinner DB. Influence of morphine on the distal oesophagus and the lower oesophageal sphincter–a manometric study. Gut. 1985; 26:802–6. [PubMed: 4018646]
23. Shakeri R, Kamangar F, Mohamadnejad M, Tabrizi R, Zamani F, Mohamadkhani A, et al. Opium use, cigarette smoking, and alcohol consumption in relation to pancreatic cancer. Medicine. 2016; 95:e3922. [PubMed: 27428185]
24. Abnet CC, Saadatian-Elahi M, Pourshams A, Boffetta P, Feizzadeh A, Brennan P, 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; 13:1068–70. [PubMed: 15184266]
25. Khademi H, Etemadi A, Kamangar F, Nouraie M, Shakeri R, Abaie B, et al. Verbal autopsy: reliability and validity estimates for causes of death in the Golestan Cohort Study in Iran. PloS One. 2010; 5:e11183. [PubMed: 20567597]
26. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Annals Oncol. 2012; 23:1880–8.
27. Hameed M, Hameed H, Erdek M. Pain management in pancreatic cancer. Cancers (Basel). 2010; 3:43–60. [PubMed: 24212605]
28. Li JH, Lin LF. Genetic toxicology of abused drugs: a brief review. Mutagenesis. 1998; 13:557–65. [PubMed: 9862186]
29. Gupta K, Kshirsagar S, Chang L, Schwartz R, Law PY, Yee D, et al. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res. 2002; 62:4491–8. [PubMed: 12154060]
30. Singleton PA, Mambetsariev N, Lennon FE, Mathew B, Siegler JH, Moreno-Vinasco L, et al. Methylnaltrexone potentiates the anti-angiogenic effects of mTOR inhibitors. J Angiogenes Res. 2010; 2:5. [PubMed: 20298531]
31. Mathew B, Lennon FE, Siegler J, Mirzapoiazova T, Mambetsariev N, Sammani S, et al. The novel role of the mu opioid receptor in lung cancer progression: a laboratory investigation. Anesth Analg. 2011; 112:558–67. [PubMed: 21156980]
32. Lennon FE, Mirzapoiazova T, Mambetsariev B, Salgia R, Moss J, Singleton PA. Overexpression of the mu-opioid receptor in human non-small cell lung cancer promotes Akt and mTOR activation, tumor growth, and metastasis. Anesthesiology. 2012; 116:857–67. [PubMed: 22343475]
33. Lennon FE, Mirzapoiazova T, Mambetsariev B, Poroyko VA, Salgia R, Moss J, et al. The Mu opioid receptor promotes opioid and growth factor-induced proliferation, migration and Epithelial Mesenchymal Transition (EMT) in human lung cancer. PloS One. 2014; 9:e91577. [PubMed: 24662916]
34. Lu J, Liu Z, Zhao L, Tian H, Liu X, Yuan C. In vivo and in vitro inhibition of human liver cancer progress by downregulation of the mu-opioid receptor and relevant mechanisms. Oncol Rep. 2013; 30:1731–8. [PubMed: 23900681]
35. Cieslinska A, Sienkiewicz-Szlapka E, Kostyra E, Fiedorowicz E, Snarska J, Wronski K, et al. μ-Opioid receptor gene (OPRM1) polymorphism in patients with breast cancer. Tumour Biol. 2015; 36:4655–60. [PubMed: 25618602]

36. Bortsov AV, Millikan RC, Belfer I, Boortz-Marx RL, Arora H, McLean SA. mu-Opioid receptor gene A118G polymorphism predicts survival in patients with breast cancer. Anesthesiology. 2012; 116:896–902. [PubMed: 22433205]

37. Peng J, Sarkar S, Chang SL. Opioid receptor expression in human brain and peripheral tissues using absolute quantitative real-time RT-PCR. Drug Alcohol Depend. 2012; 124:223–8. [PubMed: 22356890]

38. Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol. 2009; 170(4):403–13. [PubMed: 19561064]

39. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, Michaud DS, Severinsen MT, Overvad K, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2010; 126(10):2394–403. [PubMed: 19790196]

40. International Agency for Research on Cancer. Inorganic and organic lead compounds. Vol. 87. Lyon: France International Agency for Research on Cancer; 2006. IARC monographs on the evaluation of carcinogenic risks to humans.

41. Fu H, Boffetta P. Cancer and occupational exposure to inorganic lead compounds: a meta-analysis of published data. Occup Environ Med. 1995; 52(2):73–81. [PubMed: 7757170]

42. Ojajärvi IA, Partanen TJ, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, et al. Occupational exposures and pancreatic cancer: a meta-analysis. Occup Environ Med. 2000 May; 57(5):316–24. 2000. [PubMed: 10769297]

43. Mahmoodpoor A, Golzari SE. Epigenetics, opium, and cancer. Lancet Oncol. 2014; 15:e153. [PubMed: 24694638]

44. Salehi H, Sayadi AR, Tashakori M, Yazdandoost R, Soltanpoor N, Sadeghi H, et al. Comparison of serum lead level in oral opium addicts with healthy control group. Arch Iran Med. 2009; 12(6): 555–8. [PubMed: 19877747]

Table 1

Baseline characteristics of Golestan Cohort Study participants according to opium consumption.

Variable	Opium consumption			
	None	<81 nokhod-year	≥81 nokhod-year	P value
Number of participants, n (%)	41,545 (83.0)	6,773 (13.5)	1,727 (3.5)	–
Age at baseline (year), mean±SD	51.81±8.83	52.87±9.09	54.86±9.37	**<0.001**
Follow up (year), mean±SD	8.06+1.65	7.60+2.02	7.26+2.13	**<0.001**
Sex (female), n (%)	26,458 (63.7)	2,099 (31.0)	254 (14.7)	**<0.001**
Ethnicity (Turkmen), n (%)	30,693 (73.9)	5,115 (75.5)	1445 (83.7)	**<0.001**
Residence (rural), n (%)	32,516 (78.3)	5,903 (87.2)	1592 (92.2)	**<0.001**
BMI (Kg/m^2), mean ± SD	27.25±5.36	23.98±5.02	23.15±4.70	**<0.001**
Ever smoking, n (%)	4,171 (10.0)	3,298 (48.7)	1,188 (68.8)	**<0.001**
Current smoking, n (%)	3,022 (7.3)	2,845 (42.0)	1,072 (62.1)	**<0.001**
Smoking (Pack-year), mean ± SD	1.50±7.09	8.10±14.78	17.56±22.44	**<0.001**
Alcohol consumption, n (%)	802 (1.9)	629 (9.3)	298 (17.3)	**<0.001**
Diabetes mellitus, n (%)	2,902 (7.0)	486 (7.2)	56 (3.2)	**<0.001**

BMI, body mass index

Table 2

HR (95% CI) for pancreatic cancer according to opium consumption

Index	Opium use				
	None	Low dose opium use		High dose opium use	
		<81 Nokhod-year	P value	≥81 Nokhod-year	P value
N. of cases (patients)	37	9		8	
Person-year	296,781	45,006		11,103	
HR (95% CI) (model 1)	Ref.	1.44 (0.68–3.04)	0.337	4.49 (2.00–1.07)	**<0.001**
HR (95% CI) (model 2)	Ref.	1.20 (0.55–2.63)	0.642	3.43 (1.44–8.18)	**0.005**
HR (95% CI) (model 3)	Ref.	1.16 (0.52–2.55)	0.718	3.13 (1.30–7.61)	**0.011**
HR (95% CI) (model 4)	Ref.	1.10 (0.49–2.44)	0.819	2.92 (1.20–7.12)	**0.019**

COX hazard ratio adjusted for age, sex (model 1); further adjusted for cigarette smoking status (never, ever) and alcohol consumption (never, ever) (model 2); cigarette smoking status was modeled as never, former, or current (model 3); further adjusted for type 2 diabetes mellitus and BMI (model 4).

Table 3

HR (95% CI) for pancreatic cancer according to the combination of cigarette smoking and opium consumption.

Variable	Cohort participants, n (%)	Pancreatic cancer, n (%)	Model 1*		Model 2§	
			HR (95% CI)	P-value	HR (95% CI)	P-value
Smoking never/opium never	37,343 (74.7)	31 (57.4)	Ref.	–	Ref.	–
Smoking never/opium ever	4,014 (8.0)	5 (9.3)	1.25 (0.48–3.28)	0.650	1.25 (0.48–3.28)	0.650
Smoking ever/opium never	4,165 (8.3)	6 (11.1)	1.69 (0.64–4.51)	0.291	1.77 (0.63–4.96)	0.278
Smoking ever/opium ever	4,477 (9.0)	12 (22.2)	3.08 (1.37–7.97)	**0.007**	3.09 (1.24–7.74)	**0.016**
Smoking never opium < 81≠	3,472 (6.9)	3 (5.6)	0.92 (0.28–3.04)	0.886	0.92 (0.28–3.03)	0.884
Smoking never/opium ≥ 81	537 (1.1)	2 (3.7)	3.14 (0.73–13.56)	0.125	3.13 (0.73–13.51)	0.126
Smoking ever/opium < 81	3,292 (6.6)	6 (11.1)	2.22 (0.83–5.98)	0.113	2.33 (0.82–6.67)	0.114
Smoking ever/opium ≥ 81	1,182 (2.4)	6 (11.1)	5.38 (1.96–14.75)	**0.001**	5.78 (1.85–18.05)	**0.003**

*Cox hazard ratio adjusted for age and sex, alcohol consumption; type 2 diabetes mellitus; and BMI.

§Cox hazard ratio further adjusted for cigarette smoking pack-year

≠nokhod-years