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Opium; an emerging risk factor for gastric adenocarcinoma

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Abstract

Opium use has been associated with higher risk of cancers of the esophagus, bladder, larynx, and lung; however, no previous study has examined its association with gastric cancer. There is also little information on the associations between hookah (water pipe) smoking or the chewing of tobacco products and the risk of gastric cancer. In a case-control study in Golestan Province of Iran, we enrolled 309 cases of gastric adenocarcinoma (118 noncardia, 161 cardia, and 30 mixed-location adenocarcinomas) and 613 matched controls. Detailed information on long-term use of opium, tobacco products, and other covariates were collected using structured and validated lifestyle and food frequency questionnaires. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were obtained using conditional logistic regression models. Opium use was associated with an increased risk of gastric adenocarcinoma, with an adjusted OR (95% CI) of 3.1 (1.9 – 5.1), and this increased risk was apparent for both anatomic subsites (cardia and noncardia). There was a dose-response effect, and individuals with the highest cumulative opium use had the strongest association (OR: 4.5; 95%CI: 2.3-8.5). We did not find a statistically significant association between the use of any of the tobacco products and risk of gastric adenocarcinoma, overall or by anatomic subsite. We showed, for the first time, an association between opium use and gastric adenocarcinoma. Given that opium use is a traditional practice in many parts of the world, these results are of public health significance.

Keywords

Opium; Adenocarcinoma; Cardia

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Introduction

Gastric cancer is the 2nd most common cancer in men and the 4th most common cancer in women in developing countries [1]. The striking geographical variation in gastric cancer incidence and mortality, as well as the significant changes in rates over time and among migrants, suggest a strong role for environmental and life style factors in its pathogenesis [2]. Previous studies have identified *Helicobacter pylori* infection and cigarette smoking as risk factors associated with higher risk of gastric cancer while higher intake of fruits and vegetables and the use of refrigerators have shown an inverse association with gastric cancer risk [2-8].

Regular use of opium has been reported to be associated with increased risk of several cancers, including esophageal cancer [9-11], laryngeal cancer [12], bladder cancer [13-15], and lung cancer [16], but to our knowledge no epidemiologic studies of opium use and gastric cancer have been published. About 0.3-0.5% of the world's population in the 15-64 year old age group, between 12 and 21 million people, used opiates at least once in 2009 [17]. Opium is traditionally used in many South-Central Asian countries, especially Iran, Pakistan, Afghanistan and India, as well as in some areas of South-East Asia. These are also areas with some of the highest rates of gastric cancer incidence and mortality in the world. In many of these areas, hookah (water-pipe) use is also a widely practiced social habit [18], and it is estimated that 100 million people across the world smoke hookah [19]. Although numerous studies have examined the association between cigarette smoking and gastric cancer [20-22], much less is known about the associations of other types of tobacco use, such as smoking hookah or chewing tobacco, and this malignancy. These products have been shown to increase the risk of lung [23] and esophageal cancer [10, 24], and a World Health Organization Study Group has recommended more research on them [18], since the amount of evidence on their health effects is still modest [23].

In Iran, gastric cancer has the highest incidence among all cancers, excluding skin cancers [25], but it shows geographical variation in incidence across the country, with northwestern and northeastern Iran having the highest rates [3]. In the northeast of Iran, approximately 17% of individuals above the age of 40 have experienced opium use, and about 7.6% have ever smoked chewed nass (a chewing product containing tobacco, ash, and lime)[26]. We recently collected detailed data on the use of opium and several types of tobacco (cigarettes, hookah, and nass) in a case-control study of gastric cancer in Golestan Province in northeastern Iran. The purpose of the current analysis is to examine the association between these exposures and gastric cancer.

Methods

Case and control selection

Cases were enrolled from December 2004 to December 2011, in Atrak Clinic, a gastroenterology specialty clinic in Gonbad City, the largest city in Golestan Province. Case selection methods were similar to those in a previous case-control study of esophageal cancer in this area [10]. In brief, local physicians referred patients suspected of having upper gastrointestinal (GI) tract diseases to Atrak Clinic, where they underwent upper GI endoscopy. Biopsy samples of any mass or lesions were taken and reviewed by expert pathologists at the Digestive Disease Research Center, Tehran University of Medical Sciences. Patients with pathology reports of adenocarcinoma of the stomach were asked to participate in this study.

For each case, we tried to select two age, sex and neighborhood-matched controls from 50,045 healthy subjects, aged 40-75 years, who were enrolled in the Golestan Cohort Study

between January 2004 and June 2008 [26]. Cohort participants completed general and food frequency questionnaires similar to those for cases (see below), and gave blood, hair and nail samples. We have previously shown that controls from this cohort correctly reflect opium use in the neighborhoods of cancer cases, and compared to hospital controls, they provide more accurate estimates of cancer risks due to opium or tobacco consumption [11].

The study protocol was reviewed and approved by the Institutional Review Boards of the Digestive Disease Research Center of Tehran University of Medical Sciences, the US National Cancer Institute (NCI), and International Agency for Research on Cancer (IARC). A written informed consent was obtained from each study participants.

Questionnaires and physical examination

We administered two structured questionnaires, a general questionnaire and a food frequency questionnaire. The general questionnaire included detailed information on age, sex, ethnicity, place of residence, education, ownership of appliances and property (as indicators of socioeconomic status), and other potential confounders of interest. The food frequency questionnaire was previously validated in the Golestan population[27], and was used in this study to extract data for fruit and vegetable consumption.

Our general questionnaire included extensive and detailed questions about the exposures of interest in this study, i.e., opium, cigarettes, hookah, and nass. Our previous studies have shown that the responses of individuals in this population to questions regarding opium and tobacco use are reliable and valid[28]. Lifelong history of use was asked, including all starting and stopping ages, and the average amount of use in each period. Thus the questionnaires allowed for multiple rounds of using and stopping and different amounts of use in each period. Ever users of opium or tobacco products were defined as those reporting consuming the product at least once a week for a minimum of 6 months. Opium consumption was recorded using the local unit of nokhod per day, each nokhod being equal to 0.2 grams, and lifetime use was calculated as nokhod-years (nokhod used per day × duration of use in years). For cigarette smoking, pack-years were calculated, and for hookah and nass a similar measure was calculated using frequency of use per day × duration of use in years.

Biological sample collection

Each case provided 10 ml of venous blood: 5 ml in EDTA anticoagulant was stored as whole blood at −80 °C, and 5 ml without anticoagulant was centrifuged and the serum was stored at −80 °C. Controls provided a 10 ml sample of venous blood which was centrifuged and aliquoted into 500 ml straws (eight straws of plasma, four straws of buffy coat and two straws of red blood cells) and stored at −80 degree centigrade. Serum samples of cases and plasma samples of controls were used to determine seropositivity against CagA antigens of H. pylori. CagA analysis was performed in the German Cancer Research, Center, Heidelberg, Germany, using previously published method[29].

Statistical Analysis

The primary pre-specified null hypothesis was that opium use was not associated with odds of gastric cancer. The large majority of the cases 276 (83.4%) had two controls, but we were not able to match two controls to each case, because the cohort study participants, from whom controls were selected, were limited to individuals 40 – 75 years of age at cohort enrollment and to certain parts of the catchment area of the cases. As a result, 22 cases (6.6%) had only one control, and a few (n = 11) had more than two controls, because some of the selected controls did not have an adequate plasma sample, so we had to select additional controls for them. We used conditional logistic regression models (conditioned on sex and place of residence) to calculate unadjusted and adjusted odds ratios (ORs) and 95%

confidence Intervals (CIs). Because the cases and controls were not perfectly matched on age, we entered age as a covariate in the models. All models were further adjusted for ethnicity, education, wealth score, total daily fruit intake, and total daily intake of vegetables. Education and the wealth score were used as indicators of socioeconomic status. The wealth score is a composite score, created using multiple correspondence analysis of individuals' living conditions and ownership of different household assets; the methods for creating this score have been explained in a previous publication [30]. Furthermore, each of the main exposures of the study (e.g., opium) was adjusted for the other main exposures (e.g., hookah, nass, and cigarettes). Further adjustment for antibodies to *H. pylori* CagA antigen, which was strongly associated with risk of noncardia cancer, did not change the results, so it was not included in our final models.

For each exposure of interest, duration of use was calculated by summing the years of use. Cumulative use was calculated by multiplying duration of use by the amount. If the study participant used the exposure of interest intermittently during several periods of life, cumulative use was obtained by summing cumulative use during each period of use, or $Cum_j = \Sigma_{i=1}^{n} G_{ij} D_{ij}$; where G and D denote the amount and duration of use (in days), and j and i denote the study participant and the period of use, respectively. For each variable, the median cumulative use among controls was used for classification.

Patients may use opium to alleviate pain; hence associations may be due to reverse causality. Thus, we did a separate analysis, excluding those who had started opium within one year prior to the diagnosis.

Analyses were conducted for all gastric adenocarcinomas, as well as for the two main anatomic subtypes of gastric adenocarcinoma, i.e., noncardia and cardia gastric adenocarcinomas. This subgroup analysis was done because previous studies have shown that noncardia and cardia cancers may have different risk factors [31-33].

All statistical analyses were done using STATA statistical software, version11 (STATA Corp, College Station, Tx). P-values of less than 0.05 were considered as statistically significant.

Results

Our study sample consisted of 309 cases of gastric adenocarcinoma (118 noncardia, 161 cardia, and 30 mixed or unspecified site) and 613 matched controls. Table 1 shows the baseline characteristics of the cases and controls. Controls were perfectly matched to cases for gender (27% females in each group), but the mean age of cases was 1.6 years older than that of controls (65.2 versus 63.6 years). Controls were also closely, but not perfectly, matched to cases for urban/rural residence. The large majority of both cases (82.2%) and controls (73.3%) had no formal education.

Table 2 shows the results of opium use and different types of tobacco use in relation to noncardia, cardia, and all gastric adenocarcinomas. Ever opium use was associated with increased risk of noncardia, cardia, and all gastric adenocarcinomas, with adjusted ORs (95% CIs) of 3.9 (1.6-9.4), 2.8 (1.4-5.7), and 3.1 (1.9 – 5.2), respectively. Patients may start opium use to alleviate pain; hence associations may be due to reverse causality. However, when we limited our analyses to those who had started opium use at least one year prior to diagnosis, opium still showed a strong increased risk, with adjusted ORs (95% CIs) of 2.9 (1.1-7.5), 2.8 (1.4-5.6), and 2.9 (1.7-4.8) for noncardia, cardia, and all gastric adenocarcinomas, respectively. Current users had stronger increases in risk than former users, and there was a dose-response association with cumulative use of opium. In stratified

analyses, opium strongly and significantly increased the risk of cardia and noncardia adenocarcinoma in individuals who had never smoked cigarettes (data not shown).

Approximately 27% of both cases and control were ever cigarette smokers and all odds ratios were close to one (Table 2). About 5% of cases and 2% of controls reported ever smoking hookah. In unadjusted analyses, ever hookah use was associated with a significantly increased risk of noncardia adenocarcinoma, a non-significantly increased risk of cardia adenocarcinoma, and a significantly increased risk of all gastric adenocarcinomas. However, after adjustment, all odds ratios were near one, and no statistically significant difference in risk was found between cases and controls. About 13% of both cases and controls reported using nass, and nass use was not associated with risk of noncardia, cardia or all gastric adenocarcinomas.

Discussion

Our study is the first report demonstrating that opium use is associated with increased risk of gastric adenocarcinoma and its anatomic subtypes (noncardia and cardia). We also studied the association between gastric adenocarcinoma and different types of tobacco use, but did not find statistically significant associations.

There are several reasons to believe that the association between opium use and gastric cancer is causal. The associations were relatively strong, over 3-fold for noncardia cancer and over 2-fold for cardia cancer, and they showed a dose-response relationship with cumulative use of opium. Adjustments for important potential confounders, including age, ethnicity, indicators of socioeconomic status, and total fruit and vegetable intake strengthened the associations. Cases were less educated than the controls. In all, 17.6% of the cases and 26.7% of the controls had some education. However, adjusting for education and other variables related to socioeconomic status did not materially changed the results. Other reports have shown that opium can increase the risk of cancers of the esophagus [9-11], larynx [12], bladder [13-15], lung [16], and also total mortality from cancer [34]. For most participants, opium use started long before any symptoms developed, and when we excluded cases that started using opium in the year prior to their diagnosis and their matched controls, the results still showed a nearly 3-fold increased risk of all gastric adenocarcinomas among users.

Several mechanisms have been proposed for the association between opium use and cancer. Smoking opium and its alkaloid components (mainly morphine) may produce mutagens [35]. *In vitro* studies have shown that pyrolysed opium dross shows mutagenic activity in *Salmonella typhimurium* strains TA98 and TA100 [36]. Pyrolysates and alkaloids of opium have also induced sister-chromatid exchanges in mammalian cells after metabolic activation [37]. These pyrolysates also transform Syrian hamster embryo cells in culture and have carcinogenic effects in mice and hamsters following topical, subcutaneous, intratracheal or intragastric administration[38]. Nevertheless, the mechanisms for the carcinogenicity of opium are not yet well understood, and with increasing evidence showing the association between opium use and cancer, more studies are needed to elucidate the mechanisms.

Although opium use in Golestan Province appears to have declined in the past four decades [39], its prevalence in the region is still high [26]; approximately 17% of the adults participating in the Golestan Cohort reported ever using opium [11]. Therefore, if the association is causal, it may account for an important percentage of gastric cancer cases in Golestan Province. Opium and its derivatives are also used by an estimated 15 million

people across the world [17]; therefore such products may also have an important role in the causation of gastric cancer worldwide.

The association between cigarette smoking and gastric cancer has been investigated in many case-control and cohort studies. Meta-analyses summarizing these studies have shown an overall 1.5- to 2-fold increased risk of gastric cancer in cigarette smokers but there has been considerable variation among studies [20-22]. The results of our study did not show an association between cigarette smoking and gastric cancer risk. Interestingly, previous studies conducted in this area have shown only a weak association between cigarette smoking and risk of esophageal squamous cell carcinoma[10], whereas cigarettes are a very strong risk factor for this cancer elsewhere[40-42]. We are not sure why we see lower risks of both esophageal and gastric cancers associated with cigarette smoking in this area, but this may be due to low intensity or cumulative use of cigarette smoking in this area or the type of tobacco used. For example, only 14.2% and 11.1 % of our gastric adenocarcinoma cases and controls, respectively, reported over 20 pack-years of cumulative cigarette smoking, while more than 51% of gastric cancer cases and 28% of controls in Netherlands Cohort Study on Diet and Cancer (NLCS) had smoked this amount [43].

To our knowledge, there is no previous investigation of hookah or nass use in relation to gastric cancer. Hookah smoking showed apparent associations with both noncardia and cardia cancers in unadjusted models, but the adjusted results showed no significant associations. Cumulative use of hookah has previously been shown to be associated with risk of esophageal squamous cell carcinoma in this population [10]. It is possible that hookah use in fact does not cause an increased risk of gastric cancer, or that the small number of people who use hookah in this population requires a larger sample to study its effect. Therefore, our results can only be considered a first attempt at exploring this association, and they need to be combined with results from future studies. Similarly, we did not find a significant association with nass use, another form of tobacco use previously shown to be (weakly) associated with the risk of esophageal squamous cell carcinoma [10]. Oral tobacco use was not shown to increase gastric cancer risk in India [44], and it is more likely to cause more proximal cancers in the gastrointestinal tract, most notably in the oral cavity [45].

This study has several strengths, including histologic diagnosis of all cases, classification of most cases to noncardia or cardia subsites, use of population-based controls previously shown to be appropriate controls for cases referred to our clinic [11], and use of reliable and validated questionnaires. Like other case-control studies, this study is potentially prone to recall bias, and interviewer bias arising from data collection after the diagnosis. However, given that neither the study interviewers nor study participants had any preconceived hypothesis that opium could cause cancer of the stomach, significant interviewer or recall bias are not likely. Furthermore, the absence of any association with cigarette smoking, which is a better-known risk factor for gastric cancer, reduces the possibility of such biases. Another potential limitation of the study is the modest sample size in gastric cancer subcategories.

In conclusion, this first test of the hypothesis showed a direct association between opium use and gastric adenocarcinoma, including both of its anatomic subtypes. This association was strong, independent of known causes of gastric cancer, and similar to previous reports at other cancer sites, so this association may be causal. However, further human studies, animal studies, and other mechanistic studies are needed to confirm or refute this association.

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References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011; 61:69–90. [PubMed: 21296855]
2. Moy KA, Fan YH, Wang RW, Gao YT, Yu MC, Yuan JM. Alcohol and Tobacco Use in Relation to Gastric Cancer: A Prospective Study of Men in Shanghai, China. Cancer Epidem Biomar. 2010; 19:2287–97.
3. Malekzadeh R, Derakhshan MH, Malekzadeh Z. Gastric cancer in Iran: epidemiology and risk factors. Arch Iran Med. 2009; 12:576–83. [PubMed: 19877751]
4. Pakseresht M, Forman D, Malekzadeh R, Yazdanbod A, West RM, Greenwood DC, Crabtree JE, Cade JE. Dietary habits and gastric cancer risk in north-west Iran. Cancer Causes Control. 2011; 22:725–36. [PubMed: 21347819]
5. Krejs GJ. Gastric cancer: epidemiology and risk factors. Dig Dis. 2010; 28:600–3. [PubMed: 21088409]
6. Yang ZR, Liu M, Peng XL, Lei XF, Zhang JX, Dong WG. Noscapine induces mitochondria-mediated apoptosis in human colon cancer cells in vivo and in vitro. Biochemical and biophysical research communications. 2012; 421:627–33. [PubMed: 22546556]
7. Compare D, Rocco A, Nardone G. Risk factors in gastric cancer. Eur Rev Med Pharmacol Sci. 2010; 14:302–8. [PubMed: 20496539]
8. Fuccio L, Eusebi LH, Bazzoli F. Gastric cancer, Helicobacter pylori infection and other risk factors. World J Gastrointest Oncol. 2010; 2:342–7. [PubMed: 21160805]
9. Ghadirian P, Stein GF, Gorodetzky C, Roberfroid MB, Mahon GA, Bartsch H, Day NE. Oesophageal cancer studies in the Caspian littoral of Iran: some residual results, including opium use as a risk factor. Int J Cancer. 1985; 35:593–7. [PubMed: 3997280]
10. Nasrollahzadeh D, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet CC, Shakeri R, Pourshams A, Marjani HA, Nouraie M, Khatibian M, Semnani S, et al. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. Brit J Cancer. 2008; 98:1857–63. [PubMed: 18475303]
11. Shakeri R, Kamangar F, Nasrollahzadeh D, Nouraie M, Khademi H, Etemadi A, Islami F, Marjani H, Fahimi S, Sepehr A, Rahmati A, Abnet CC, 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:e32711. [PubMed: 22396792]
12. Mousavi MR, Damghani MA, Haghdoust AA, Khamesipour A. Opium and risk of laryngeal cancer. Laryngoscope. 2003; 113:1939–43. [PubMed: 14603052]
13. Hosseini SY, Safarinejad MR, Amini E, Hooshyar H. Opium consumption and risk of bladder cancer: A case-control analysis. Urol Oncol-Semin Ori. 2010; 28:610–16.
14. Behmard S, Sadeghi A, Mohareri MR, Kadivar R. Positive association of opium addiction and cancer of the bladder. Results of urine cytology in 3,500 opium addicts. Acta Cytol. 1981; 25:142–6. [PubMed: 6941612]
15. Sadeghi A, Behmard S, Vesselinovitch SD. Opium: a potential urinary bladder carcinogen in man. Cancer. 1979; 43:2315–21. [PubMed: 455221]
16. Masjedi MR, Naghan PA, Taslimi S, Yousefifard M, Ebrahimi SM, Khosravi A, Karimi S, Hosseini M, Mortaz E. Opium Could Be Considered an Independent Risk Factor for Lung Cancer: A Case-Control Study. Respiration. 2012
17. UNODC. World Drug Report_2011: United Nations Office on Drugs and Crime. 2011.
18. TobReg Wsgotpr. Waterpipe tobacco smoking: Health effects, research needs and recommended actions by regulators: World Health Organization (WHO). 2005.

19. Mohammadpour-Ahranjani B, Rashidi A, Karandish M, Eshraghian MR, Kalantari N. Prevalence of overweight and obesity in adolescent Tehrani students, 2000-2001: an epidemic health problem. Public Health Nutr. 2004; 7:645–8. [PubMed: 15251055]

20. Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R, Lunet N. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Cause Control. 2008; 19:689–701.

21. Tredaniel J, Boffetta P, Buiatti E, Saracci R, Hirsch A. Tobacco smoking and gastric cancer: Review and meta-analysis. International Journal of Cancer. 1997; 72:565–73.

22. Tramacere I, La Vecchia C, Negri E. Tobacco smoking and esophageal and gastric cardia adenocarcinoma: a meta-analysis. Epidemiology. 2011; 22:344–9. [PubMed: 21330928]

23. Akl EA, Gaddam S, Gunukula SK, Honeine R, Abou Jaoude P, Irani J. The effects of waterpipe tobacco smoking on health outcomes: a systematic review. Int J Epidemiol. 2010; 39:834–57. [PubMed: 20207606]

24. Mahboubi E, Kmet J, Cook PJ, Day NE, Ghadirian P, Salmasizadeh S. Oesophageal cancer studies in the Caspian Littoral of Iran: the Caspian cancer registry. Br J Cancer. 1973; 28:197–214. [PubMed: 4743904]

25. Mousavi SM, Gouya MM, Ramazani R, Davanlou M, Hajsadeghi N, Seddighi Z. Cancer incidence and mortality in Iran. Ann Oncol. 2009; 20:556–63. [PubMed: 19073863]

26. Pourshams A, Khademi H, Malekshah AF, Islami F, Nouraei M, Sadjadi AR, Jafari E, Rakhshani N, Salahi R, Semnani S, Kamangar F, Abnet CC, et al. Cohort Profile: The Golestan Cohort Studya prospective study of oesophageal cancer in northern Iran. Int J Epidemiol. 2010; 39:52–59. [PubMed: 19332502]

27. Malekshah AF, Kimiagar M, Saadatian-Elahi M, Pourshams A, Nouraie M, Goglani G, Hoshiarrad A, Sadatsafavi M, Golestan B, Yoonesi A, Rakhshani N, Fahimi S, et al. Validity and reliability of a new food frequency questionnaire compared to 24 h recalls and biochemical measurements: pilot phase of Golestan cohort study of esophageal cancer. European Journal of Clinical Nutrition. 2006; 60:971–77. [PubMed: 16465196]

28. Abnet CC, Saadatian-Elahi M, Pourshams A, Boffetta P, Feizzadeh A, Brennan P, Taylor PR, Kamangar F, Dawsey SM, Malekzadeh R. Reliability and validity of opiate use self-report in a population at high risk for esophageal cancer in Golestan, Iran. Cancer Epidem Biomar. 2004; 13:1068–70.

29. Gao L, Michel A, Weck MN, Arndt V, Pawlita M, Brenner H. Helicobacter pylori infection and gastric cancer risk: evaluation of 15 H. pylori proteins determined by novel multiplex serology. Cancer Res. 2009; 69:6164–70. [PubMed: 19602590]

30. Islami F, Kamangar F, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, Abedi-Ardekani B, Merat S, Nasseri-Moghaddam S, Semnani S, Sepehr A, Wakefield J, Moller H, et al. Socio-economic status and oesophageal cancer: results from a population-based case-control study in a high-risk area. Int J Epidemiol. 2009; 38:978–88. [PubMed: 19416955]

31. Nouraie M, Pietinen P, Kamangar F, Dawsey SM, Abnet CC, Albanes D, Virtamo J, Taylor PR. Fruits, vegetables, and antioxidants and risk of gastric cancer among male smokers. Cancer Epidem Biomar. 2005; 14:2087–92.

32. Webb PM, Law M, Varghese C, Forman D, Yuan JM, Yu M, Ross R, Limberg PJ, Mark SD, Taylor PR, Dawsey SM, Qiao YL, et al. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut. 2001; 49:347–53. [PubMed: 11511555]

33. Kamangar F, Dawsey SM, Blaser MJ, Perez-Perez GI, Pietinen P, Newschaffer CJ, Abnet CC, Albanes D, Virtamo J, Taylor PR. Opposing risks of gastric cardia and noncardia gastric adenocarcinomas associated with Helicobacter pylori seropositivity. J Natl Cancer I. 2006; 98:1445–52.

34. Khademi H, Malekzadeh R, Pourshams A, Jafari E, Salahi R, Semnani S, Abaie B, Islami F, Nasseri-Moghaddam S, Etemadi A, Byrnes G, Abnet CC, et al. Increased Mortality from Opium Use in the Golestan Cohort Study: A Prospective Cohort Study of 50,000 Adults. Bmj. 2012

35. Malaveille C, Friesen M, Camus AM, Garren L, Hautefeuille A, Bereziat JC, Ghadirian P, Day NE, Bartsch H. Mutagens Produced by the Pyrolysis of Opium and Its Alkaloids as Possible Risk-

Factors in Cancer of the Bladder and Esophagus. Carcinogenesis. 1982; 3:577–85. [PubMed: 7046981]

36. Hewer T, Rose E, Ghadirian P, Castegnaro M, Malaveille C, Bartsch H, Day N. Ingested mutagens from opium and tobacco pyrolysis products and cancer of the oesophagus. Lancet. 1978; 2:494–6. [PubMed: 79865]
37. Perry PE, Thomson EJ, Vijayalaxmi, Evans HJ, Day NE, Bartsch H. Induction of SCE by opium pyrolysates in CHO cells and human peripheral blood lymphocytes. Carcinogenesis. 1983; 4:227–30. [PubMed: 6825211]
38. Friesen M, O'Neill IK, Malaveille C, Garren L, Hautefeuille A, Cabral JR, Galendo D, Lasne C, Sala M, Chouroulinkov I, 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]
39. Khademi H, Kamangar F. Esophageal cancer incidence trends in northeastern iran: comparing rates over 36 years. Arch Iran Med. 2012; 15:194–5. [PubMed: 22424033]
40. Freedman ND, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, Schatzkin A. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol. 2007; 165:1424–33. [PubMed: 17420181]
41. Tuyns AJ. Oesophageal cancer in non-smoking drinkers and in non-drinking smokers. Int J Cancer. 1983; 32:443–4. [PubMed: 6618707]
42. Brown LM, Hoover R, Silverman D, Baris D, Hayes R, Swanson GM, Schoenberg J, Greenberg R, Liff J, Schwartz A, Dosemeci M, Pottern L, et al. Excess incidence of squamous cell esophageal cancer among US black men: Role of social class and other risk factors. Am J Epidemiol. 2001; 153:114–22. [PubMed: 11159155]
43. Steevens J, Schouten LJ, Goldbohm RA, van den Brandt PA. Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: a prospective cohort study. Gut. 2010; 59:39–48. [PubMed: 19828467]
44. Gajalakshmi CK, Shanta V. Lifestyle and risk of stomach cancer: a hospital-based case-control study. Int J Epidemiol. 1996; 25:1146–53. [PubMed: 9027518]
45. Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. Lancet Oncol. 2008; 9:667–75. [PubMed: 18598931]

While several, mostly recent, studies have shown associations between opium use and higher risk of cancers of the esophagus, bladder, larynx, and lung, no previous study has yet studied the association between opium use and gastric adenocarcinoma. Therefore, our study is the first to examine and show such an association. Given that opium use is a traditional practice in many parts of the world, these results are of public health significance.

Table 1

Baseline characteristics of cases and matched controls

	Matched controls	Noncardia adenocarcinoma	Matched controls	Cardia adenocarcinoma	Matched controls	All gastric adenocarcinoma *
N	231	118	323	161	613	309
Age (years), mean (SD)	62.5(9.5)	63.7(10.6)	64.5(8.9)	66.4(10.9)	63.6(9.1)	65.2(10.7)
Female gender, N (%)	65(28.1)	36(30.5)	83(25.7)	38(23.6)	167(27.2)	83(26.9)
Urban residence, N (%)	73(31.6)	38(32.2)	96(29.7)	52(32.5)	192(31.3)	100(32.5)
Ethnicity, N (%)						
Turkmen	118(51.1)	39(33.1)	216(66.8)	92(57.1)	368(60.0)	145(46.9)
Fars	35(15.2)	35(29.7)	39(12.1)	22(13.7)	87(14.2)	62(20.1)
Turk	39(16.9)	19(16.1)	32(9.9)	21(13)	78(12.8)	47(15.2)
Sistani	24(10.4)	13(11)	30(9.3)	18(11.2)	57(9.3)	33(10.7)
Others	15(6.5)	12(10.1)	6(1.9)	8(5)	23(3.7)	22(7.1)
Education, N (%)						
Some education	60(26.0)	21(17.8)	88(27.2)	27(16.8)	164(26.7)	55(17.8)
No formal education	171(74.0)	97(82.2)	235(72.8)	134(83.2)	449(73.3)	254(82.2)
Total fruit consumption (g/day), mean (SD)	136.5(122.9)	157.7(133.2)	142.0(115.5)	171.3(174.0)	139.2(116.5)	166.0(155.5)
Total vegetable consumption (g/day), mean (SD)	184.8(91.9)	172.9(103.6)	184.4(105.2)	174.4(98.2)	185.7(99.5)	176.7(103.1)
Homeownership, N (%)	221(95.7)	105(89.7)	316(97.8)	159(94.4)	594(96.9)	285(92.2)
Home size (m^2), mean(SD)	103(49.9)	99.7(94.5)	107.8(53.1)	101.2(48.7)	105.9(51.7)	100.5(70.0)
Mean wealth score (SD)	42.3(215.5)	1.8(222.8)	55.1(221.9)	42.8(223.1)	50.7(219.9)	28.7(223.1)

* All gastric adenocarcinomas (n = 309) include noncardia (n = 118) and cardia (n = 161) adenocarcinomas, as well adenocarcinomas of mixed or unknown site (n = 30).

Table 2

Opium and different types of tobacco use in relation to gastric noncardia adenocarcinoma, gastric cardia adenocarcinoma, and all gastric adenocarcinomas

	Gastric noncardia adenocarcinoma (GNCA)				Gastric cardia adenocarcinoma (GCA)				All Gastric adenocarcinoma (GA)			
	Matched Controls N (%)	GNCA N (%)	Unadjusted OR (95%CI) for GNCA	Adjusted* OR (95%CI) for GNCA	Matched Controls N (%)	GCA N (%)	Unadjusted OR (95%CI) for GCA	Adjusted *OR (95%CI) for GCA	Matched Controls N (%)	GA N (%)	Unadjusted OR (95%CI) for GA	Adjusted *OR (95%CI) for GA
Opium use												
Never	180(77.9)	72(61.0)	Referent	Referent	256(79.3)	110(68.3)	Referent	Referent	482(78.6)	200(64.7)	Referent	Referent
Ever	51(22.1)	46(39.0)	3.0(1.6-5.3)	3.9(1.6-9.4)	67(20.7)	51(31.7)	1.8(1.1-2.9)	2.8(1.4-5.7),	131(21.4)	109(35.3)	2.3(1.6-3.2)	3.1(1.9-5.2)
Cumulative * use**												
Never used	180(77.9)	72(61.0)	Referent	Referent	256(79.3)	110(68.3)	Referent	Referent	482(78.6)	200(64.7)	Referent	Referent
≤median (29 unit-years)**	33(14.3)	35(29.7)	2.3(1.1-4.6)	3.5(1.3-8.8)	32(9.9)	43(26.7)	1.9(1.1-3.4)	2.1(0.9-4.8)	82(13.4)	87(28.2)	2.0(1.3-3.1)	2.5(1.4-4.3)
>median	18(7.8)	11(9.3)	4.1(1.9-9.1)	5.7(1.5-21.0)	35(10.8)	8(5.0)	1.8(1.1-3.2)	3.9(1.6-9.4)	49(8.0)	22(7.1)	2.6(1.7-4.0)	4.5(2.3-8.5)
Cigarette smoking												
Never	168(72.7)	82(70.1)	Referent	Referent	234(72.4)	120(74.5)	Referent	Referent	447(72.9)	224(72.7)	Referent	Referent
Ever	63(27.3)	36(29.9)	1.2(0.7-2.1)	0.9(0.4-2.0)	89(27.6)	41(25.5)	0.8(0.5-1.4)	0.8(0.4-1.5)	166(27.1)	85(27.3)	1.02(0.7-1.4)	0.8(0.5-1.3)
Cumulative use												
Never used	168(72.7)	82(70.1)	Referent	Referent	234(72.4)	120(74.5)	Referent	Referent	447(72.9)	224(72.7)	Referent	Referent
≤median (15 pack-years)**	30(13)	12(9.4)	0.8(0.4-1.9)	0.7(0.3-2.0)	45(13.9)	18(11.2)	0.7(0.4-1.4)	0.7(0.3-1.6)	85(13.9)	33(10.7)	0.7(0.4-1.2)	0.6(0.3-1.2)
>median	33(14.3)	24(17.9)	1.5(0.7-2.9)	1.1(0.4-3.0)	44(13.6)	23(14.3)	1.1(0.5-1.7)	0.9(0.4-2.0)	81(13.2)	52(16.6)	1.2(0.8-1.9)	1.1(0.5-1.8)
Hookah smoking												
Never	226(97.8)	110(93.2)	Referent	Referent	316(97.8)	154(95.6)	Referent	Referent	600(97.9)	294(95.1)	Referent	Referent
Ever	5(2.2)	8(6.8)	3.2(1.04-9.7)	4.0(0.4-33.6)	7(2.2)	7(4.4)	2.0(0.6-6.3)	0.7(0.1-3.7)	13(2.1)	15(4.9)	2.3(1.1-5.1)	1.1(0.3-3.3)
Cumulative use												
Never used	226(97.8)	110(93.2)	Referent	Referent	316(97.8)	154(95.6)	Referent	Referent	600(97.9)	294(95.1)	Referent	Referent
≤median (50 hookah-years)**	3(1.3)	4(3.4)	2.6(0.5-11.9)	3.3(0.1-77.2)	4(1.24)	3(1.9)	1.7(0.3-7.7)	0.3(0.03-3.4)	7(1.1)	7(2.3)	2.1(0.7-6.1)	0.8(0.1-4.5)
>median	2(0.9)	4(3.4))	4.0(0.73-21.8)	4.6(0.2-84.2)	3(0.93)	4(2.5)	2.5(0.5-11.5)	1.4(0.1-11.8)	6(1.0)	(8(2.6)	2.6(0.9-7.6)	1.3(0.3-5.4)

	Gastric noncardia adenocarcinoma (GNCA)				Gastric cardia adenocarcinoma (GCA)				All Gastric adenocarcinoma (GA)			
	Matched Controls N (%)	**GNCA N (%)**	**Unadjusted OR (95%CI) for GNCA**	**Adjusted* OR (95%CI) for GNCA**	**Matched Controls N (%)**	**GCA N (%)**	**Unadjusted OR (95%CI) for GCA**	**Adjusted *OR (95%CI) for GCA**	**Matched Controls N (%)**	**GA N (%)**	**Unadjusted OR (95%CI) for GA**	**Adjusted *OR (95%CI) for GA**
Nass chewing												
Never	203(87.9)	99(83.9)	Referent	Referent	283(87.6)	143(88.8)	Referent	Referent	538(87.8)	268(86.7)	Referent	Referent
Ever	28(12.1)	19(16.1)	1.5(0.7-3.0)	0.8(0.3-2.3)	40(12.3)	18(11.2)	0.8(0.4-1.6)	0.6(0.2-1.5)	75(12.2)	41(13.3)	1.1(0.7-1.7)	0.6(0.3-1.2)
Cumulative use												
Never used	203(87.9)	99(83.9)	Referent	Referent	283(87.6)	143(88.8)	Referent	Referent	538(87.8)	268(86.7)	Referent	Referent
≤median (120 nass-years)**	17(7.4)	8(6.7)	1.1(0.4-2.6)	0.2(0.1-1.1)	22(6.8)	7(4.4)	0.6(0.2-1.5)	0.3(0.1-1.2)	42(6.8)	17(5.5)	0.8(0.4-1.5)	0.3(0.1-0.7)
>median	11(4.7)	11(9.3)	2.4(0.9-6.5)	2.7(0.7-11.1)	18(5.5)	11(6.8)	1.1(0.5-2.7)	1.1(0.3-3.8)	33(5.4)	24(7.8)	1.5(0.8-2.7)	1.4(0.6-3.3)

95%CI=95% confidence interval; OR=odds ratio. ORs were obtained from conditional logistic regression models.

*Adjusted for age, ethnicity, education, fruit consumption, vegetable consumption, socioeconomic status, and in each case for the other three main variables (eg. opium use was also adjusted for cigarette, hookah and nass use, etc.);

**Median in the control subjects was used as the dividing cut point.

***Cumulative use was calculated by multiplying intensity of use (per day) by duration of use (in years).