

# Opium: An emerging risk factor for gastric adenocarcinoma

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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.

Gastric cancer is the second most common cancer in men and the fourth most common cancer in women in developing countries.<sup>1</sup> 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.<sup>2</sup> 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.<sup>2–8</sup>

Regular use of opium has been reported to be associated with increased risk of several cancers, including esophageal

cancer,<sup>9–11</sup> laryngeal cancer,<sup>12</sup> bladder cancer<sup>13–15</sup> and lung cancer,<sup>16</sup> 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.<sup>17</sup> 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,<sup>18</sup> and it is estimated that 100 million people across the world smoke hookah.<sup>19</sup> Although numerous studies have examined the association between cigarette smoking and gastric cancer,<sup>20–22</sup> 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<sup>23</sup> and esophageal cancer,<sup>10,24</sup> and a World Health Organization Study Group has recommended more research on them,<sup>18</sup> as the amount of evidence on their health effects remains modest.<sup>23</sup>

In Iran, gastric cancer has the highest incidence among all cancers, excluding skin cancers,<sup>25</sup> but it shows geographical variation in incidence across the country, with northwestern and northeastern Iran having the highest rates.<sup>3</sup> In the

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**What's new?**

Opium use has been associated with higher rates of various cancers, and this study is the first to look at the relationship between opium use and gastric cancer risk. The authors collected information from 309 gastric cancer cases and almost twice that many age, gender and neighborhood-matched controls about their opium use, among other lifestyle factors. Those that had ever used opium were three times more likely to have contracted gastric cancer. They found no association between gastric cancer and cigarette smoking, which is a more well-known risk factor.

northeast of Iran, ~17% of individuals above the age of 40 have experienced opium use, and about 7.6% have ever used nass (a chewing product containing tobacco, ash and lime).<sup>26</sup> 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 north-eastern Iran. The purpose of our analysis is to examine the association between these exposures and gastric cancer.

**Material and 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.<sup>10</sup> 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 our 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.<sup>26</sup> 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.<sup>11</sup>

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<sup>27</sup> and was used in our study to extract data for fruit and vegetable consumption.

Our general questionnaire included extensive and detailed questions about the exposures of interest in our 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.<sup>28</sup> 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 g, 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°C. 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.<sup>29</sup>

**Statistical analysis**

The primary prespecified 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,