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Neglected role of hookah and opium in gastric carcinogenesis: A Cohort Study on risk factors and attributable fractions

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Abstract

A recent study showed an association between hookah/opium use and gastric cancer but no study has investigated the relationships with gastric precancerous lesions. We examined the association between hookah/opium and gastric precancerous lesions and subsequent gastric cancer.

In a population-based cohort study, 928 randomly selected, healthy, *Helicobacter pylori* infected subjects in Ardabil Province, Iran, were followed for 10 years. The association between baseline precancerous lesions and lifestyle risk factors (including hookah/opium) was analyzed using logistic regression and presented as odds ratios (ORs) and 95% confidence intervals (CIs). We also calculated hazard ratio (HRs) and 95% CIs for the associations of lifestyle risk factors and endoscopic and histological parameters with incident gastric cancers using Cox regression models. Additionally, the proportion of cancers attributable to modifiable risk factors was calculated.

During 9,096 person-years of follow-up, 36 new cases of gastric cancer were observed (incidence rate: 3.96/1000 persons-years). Opium consumption was strongly associated with baseline antral (OR:3.2;95%CI:1.2–9.1) and body intestinal metaplasia (OR:7.3;95%CI:2.5–21.5). Opium (HR: 3.2;95%CI:1.4–7.7), hookah (HR:3.4;95%CI:1.7–7.1) and cigarette use (HR:3.2;95%CI:1.4–7.5), as well as high salt intake, family history of gastric cancer, gastric ulcer and histological atrophic gastritis and intestinal metaplasia of body were associated with higher risk of gastric cancer. The fraction of cancers attributable jointly to high salt, low fruit intake, smoking (including hookah) and opium was 93% (95%CI:83–98).

Hookah and opium use are risk factors for gastric cancer, as well as for precancerous lesions. Hookah, opium, cigarette and high salt intake are important modifiable risk factors in this high incidence gastric cancer area.

Keywords

Gastric cancer; Precancerous lesions; *Helicobacter pylori*; Smoking; Hookah; Opium

INTRODUCTION

Gastric cancer holds a special place among worldwide malignancies in terms of both mortality and incidence, particularly in Asia. It constitutes the fourth common cause of cancer incidence and the second cause of cancer-related death.^{1, 2} Gastric cancer is the first and third most common cancer in Iranian men and women, respectively.^{3,4} Ardabil province, located to the west of the Caspian Sea littoral, has one of the highest worldwide incidence rates of gastric cancer and a rising trend compared to previous reports.³⁻⁷

The classic pathogenesis of non-cardia gastric cancer and a group of cardia cancers follows a slow progression from chronic gastritis through atrophic gastritis and intestinal metaplasia to dysplasia and eventually, adenocarcinoma.⁸ Although *Helicobacter pylori* (*H.pylori*) is essential for initiation of the cascade,⁹ remarkable geographical variations in gastric cancer incidence and mortality worldwide suggest a potential role for other lifestyle and genetic risk factors in the course of this malignancy.² Current knowledge on lifestyle and dietary risk factors of gastric cancer leaves no doubt about the role of well established factors including excess salt intake,¹⁰ low intake of fresh fruit/vegetables¹¹ and smoking.^{12,13}

A number of studies have reported associations between opium use and different malignancies, namely of esophagus,^{14,15} bladder,¹⁶ lung,¹⁷ and larynx.¹⁸ More recently, Shakeri et al showed a higher risk of gastric cancer associated with opium.¹⁹ Hookah, a traditional smoking instrument in the Middle East, is another possible risk factor for gastric cancer and a recent report indicates growing popularity of hookah in young population of Western countries.²⁰ Although largely believed by the public to be less harmful than cigarettes, the same report by Shakeri et al suggests hookah's association with gastric cancer in Iran.¹⁹ Based on the growing epidemiological evidence on the role of opium and hookah, and lack of detailed mechanistic studies on the topic, a World Health Organization (WHO) study group has encouraged investigators for further research on hookah/opium association with different types of human malignancies, including gastric cancer.^{21,22}

We aimed to investigate the factors associated with gastric precancerous and malignant lesions, including the neglected risk factors, such as hookah and opium, in a population-based, follow-up study of *H.pylori* infected subjects. As this study is one of the few investigations with baseline histological information, we could evaluate the association between baseline precancerous lesions (atrophic gastritis and intestinal metaplasia) and baseline lifestyle risk factors. Second, we could study the impact of precancerous lesions and lifestyle risk factors on the development of gastric cancer in *H.pylori* infected subjects.

Additionally, our cohort findings enabled us to calculate the fraction of incident cancers attributable to each preventable risk factor (attributable fraction).

METHODS & MATERIALS

Study Population

This population-based follow-up study took place in Ardabil province, on the western littoral of the Caspian Sea in Iran. Study participants were chosen through simple random selection from permanent residents of urban and rural areas in Ardabil (province capital) and Meshkinshahr counties, who were aged 40 years or more. The exclusion criteria were: participant's refusal, known gastrointestinal, cardiac or respiratory disease, and pregnancy. Presence of mild dyspepsia symptoms without a definite prescription by a physician was not an exclusion criterion. All participants were informed about the risks and benefits of the study and signed the informed consent forms. Out of 1,122 subjects invited, 1,011 (91.5%) consented to endoscopy. As all cancer patients were *H.pylori* positive, for the current analysis, we only included those 928 (91.8%) participants infected with *H.pylori*, based on a positive test result in either histology or rapid urease test.

Baseline measurements & data handling

Before endoscopy, trained physicians recorded all data pertaining to gastric cancer risk factors using validated structured questionnaires. Participants with a history of gastric cancer in a first-degree relative were considered as having a positive history for gastric cancer. Cigarette, hookah and opium users were defined as individuals who used the respective item at least once a week for the last 6 months. Excessive salt intake was defined as consuming more than 6 gram/day salt, and low fruit/vegetables intake was defined as eating less than 400 gram/day. The subjects subsequently underwent upper gastrointestinal endoscopy and at least one biopsy was taken from standard sites of incisura angularis and lesser and greater curvatures of antrum and corpus. Samples were stained specifically for *H.pylori* with Loeffler's Methylene blue and Warthin Starry stain. The histological results were reported according to the Updated Sydney Classification of Gastritis in 2001 and rechecked in 2011.²³

Follow-up

Study participants were followed for 10 years by Aras Clinic, which is properly equipped for diagnosis and treatment of gastrointestinal disorders and has sufficient facilities for preservation of biologic specimen. Local cancer and death registries, established at the onset of the cohort study, contributed to the follow up process.⁶ We regularly searched the relevant cancer and death registration systems to extract the time of gastric cancer events in participants of this study. The search also covered cancer and death registries of the neighboring provinces and the country's capital, Tehran, to minimize the chance of missing cases. Trained physicians directly contacted all participants (or their next of kin) for whom no records were found in above registries in order to determine their health status. Contacts were made on a yearly basis. Uncertain causes of death were further investigated using a locally validated, modified version of WHO adult verbal autopsy questionnaire.²⁴

Cancer Diagnoses

Cancer diagnoses were based on histology of specimen collected on endoscopy or surgery. If unavailable, other alternatives were used: contacting radiologists, reading physician reports (endoscopy, clinical diagnosis) and reading death reports, in decreasing order of priority. The vast majority (90%) of cancer diagnoses in our study were based on histology; 8.3% based on clinical diagnosis and only one case on death report. The location and histological type of cancer were classified using ICD-O-3 and Lauren system, when available.

Statistical Methods

The associations between baseline lifestyle risk factors and baseline precancerous lesions (atrophic gastritis and intestinal metaplasia) as main outcome were investigated using logistic regression models; the odds ratios (ORs) and 95% CIs were adjusted for relevant confounders. Cox regression models were used to calculate cancer risk during the follow up period in *H. pylori* infected subjects. The risk estimates were adjusted for all relevant confounders in separate models and were presented as hazard ratio (HRs) and 95% confidence interval (95% CIs). Results of multivariable analyses were presented only for variables that showed statistically significant associations with the outcomes of interest in age-adjusted models. The attributable fraction (AF) for modifiable risk factors (smoking (including hookah), opium, high salt intake, and low fruit/vegetables consumption) was calculated using Miettinen's formula.²⁵

$$AF_p = P(RR_a - 1)RR_a$$

where RR_a and P are adjusted relative risk and the exposure prevalence among these cases, respectively. The combined AF (AF_c) was calculated using.²⁵

$$AF_c = 1 - \prod_{i=1}^n (1 - AF_i)$$

The confidence interval of AF was quantified with the simulation technique incorporating sources of uncertainty of RR and exposure prevalence estimates obtained from our cohort.

Statistical analyses were conducted using SPSS version 19 (IBM Corp., NY, USA). All tests throughout the article were 2-sided, and p values < 0.05 were considered as statistically significant.

Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee and the Institutional Review Board of Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences.

RESULTS

Nine hundred and twenty eight participants including in this study (49.1% men) were followed up for an average of 121.8 months (range:10–132 months), during which 121 (13.0%) subjects died, and 42 (4.5%) subjects were lost to follow-up. Participants were followed up for a total duration of 9,096 person-years, during which, 36 participants were diagnosed with gastric cancer, yielding an incidence rate of 3.96/1000 persons per year.

Table 1 presents the details of the main demographics, risk factors, histological and endoscopic findings. Endoscopy revealed no significant abnormalities in only 29 (3.1%) subjects. A total of 847 (91.3%) participants had some degrees of gastritis. Evidence of active duodenal or gastric ulcer or both was found in 18 (1.9%), 28 (3.0%), and 6 (0.6%) participants, respectively. The cohort participants showed a broad spectrum of histological abnormalities other than cancer at the baseline examination (Table 1). Chronic gastritis (either mononuclear or polymorphonuclear cells infiltration) was the main histological finding in 417 (44.9%) of subjects. Atrophic gastritis (any grade) and intestinal metaplasia were the most advanced pathological changes in 372 (40.1%) and 129 (13.9%) of participants, respectively. Only 10 (1.08%) people had nonspecific minimal changes (normal histology) and no dysplasia cases were found in this study.

As detailed in Table 2, the incidence rate of cancer in those with positive family history was 12.5/1000 person-years, whereas it was as low as 1.7/1000 person-years in other participants. Among lifestyle factors, smoking tobacco increased the incidence rate of cancer significantly (7.8 vs.1.4/1000 person-years). Although opium use (mainly in the form of smoking) was not common in the study population (1.9%), it was significantly associated with a higher incidence rate of gastric cancer (24.3 vs. 3.5/1000 person-years). High salt intake (>6 gram/day) increased the incidence rate of cancer significantly (4.5 vs. 1.1/1000 person-years), but the effect of lower intake of fruit/vegetables on cancer risk was not statistically considerable. Amongst endoscopic findings, active gastric ulcer was associated with an increased cancer incidence; 29.8 vs. 3.2/1000 person-years. Having either atrophic gastritis (7.6 vs.1.4/1000 person-years) or intestinal metaplasia (19.5 vs.1.4/1000 person-years) in histological examination of any of gastric biopsies posed subjects at higher risk of cancer (Table 2).

The associations between lifestyle risk factors and gastric precancerous lesions were investigated using baseline histological findings. The antral atrophic gastritis was not associated with any of lifestyle factors, but atrophic gastritis of body mucosa was associated with lower intake of fruit/vegetables in both age-adjusted (OR:1.7,95%CI:1.2–2.3) and multivariable models (OR:1.7,95%CI:1.2–2.4; Table 3). Antral Intestinal metaplasia was associated with hookah use in age-adjusted model (OR:1.9,95%CI:1.01–3.5), but not in the multivariable model. There were strong associations between opium use (OR:3.29,95%CI: 1.2–9.1) and high salt intake (OR:2.55,95%CI:1.3–4.9) and antral intestinal metaplasia in both age-adjusted and multivariable models. Also, Intestinal metaplasia of gastric body was significantly associated with opium use in age-adjusted (OR:6.8,95%CI:2.5–18.8) and multivariable (OR=7.3,95%CI:2.5–21.5) models. Finally, there was also a significant

association between lower intake of fruit/vegetables and gastric body intestinal metaplasia in multivariable analysis (OR:2.1, 95%CI:1.05–4.1).

The relationship between gastric cancer and different potential factors was calculated using Cox proportional hazard models. The risk of cancer was significantly higher in subjects with a family history of gastric cancer in fully adjusted models (HR:5.7,95%CI:2.8–11.6; Table 4). The main lifestyle risk factors, including cigarette smoking (HR:3.2,95%CI:1.4–7.5), hookah smoking (HR:3.4,95%CI:1.7–7.1), and opium use (HR:3.2,95%CI:1.4–7.7) were associated with higher risk of cancer with similar magnitude of associations in fully adjusted models. Among dietary habits, high salt intake increased the risk of cancer (HR:4.9, 95%CI: 1.2–20.3). Male gender, alcohol, and low intake of fruit/vegetables were not associated with a higher risk of cancer.

Some endoscopic and histological parameters were also associated with higher risk of gastric cancer in Cox regression models (Table 5). Gastric ulcer was a strong risk determinant (HR:9.0, 95%CI:3.3–24.8). Among histological changes, atrophic gastritis and intestinal metaplasia of antrum showed increased risk of cancer in age-adjusted but not in fully adjusted regression models. In contrast, both atrophic gastritis and intestinal metaplasia of gastric body increased the risk of gastric cancer even in fully adjusted models, and the risk increased from lower to higher severity of histological changes (p value for trend=0.036 for atrophic gastritis and 0.001 for intestinal metaplasia). When the same analyses were done on subgroups of cancer located at cardia or non-cardia sites, the results did not change (data not shown). Furthermore, in analyses by histological subtypes of adenocarcinoma (intestinal versus diffuse type), the difference between groups was not significant as only few cases had the diffuse subtype (9 out of 36 cases) (data not shown).

Finally, we calculated the attributable fraction (AF) relevant to each factor. A great majority (AF:70.6%,95%CI:32.7–90.2) of gastric cancer was attributable to excess salt intake (Table 6). Smoking (including hookah) was the second most preventable risk factor with an AF of 62.0% (95%CI: 47.2–75.1). Although opium was strongly associated with gastric cancer, its lower prevalence among study population made it responsible for 8.3% (95%CI:2.1–16.0) of cancers. The joint effect of high salt intake, smoking and low intake of fruit/vegetables 92.3% (95%CI:81.4–97.9). Adding opium to the combination had little influence on the joint effect (93.0%,95% CI:82.9–98.1).

DISCUSSION

This population-based study was conducted on 928 adults, aged over 40 years, all of whom were infected with *H.pylori* on baseline assessments but had never sought medical consultation for digestive disorders except for intermittent dyspepsia. The ten year long follow-up, equal to 9,096 person-years, discovered 36 cases of gastric cancer (incidence: 3.96/1000 person years). Both hookah and opium were found to be strongly associated with gastric cancer, as well as atrophic gastritis and intestinal metaplasia. In addition, high salt intake, family history of gastric cancer, gastric ulcer and histological atrophic gastritis and intestinal metaplasia were associated with higher risk of gastric cancer. Moreover, approximately 93% of gastric cancers were theoretically attributable to the joint effects of

high salt intake, low fruit intake, smoking (any type) and opium. The current study is unique as access to data of lifestyle factors along with histological status of the baseline assessments allowed a mechanistic insight on gastric cancer.

We evaluated the association of two forms of smoking, cigarette and hookah, with gastric cancer in our cohort. A significantly higher risk of gastric cancer in participants with a previous or current history of cigarette smoking is consistent with previous findings from the same population as well as other investigations in different populations and with various study designs.^{26, 27} Hookah is gaining popularity among the youth, partly due to the common belief that it is safer than cigarettes. Nevertheless, we found a 3-fold higher risk of gastric cancer. An association between hookah smoking and gastric cancer has also been shown in another study.¹⁹ The mechanisms by which hookah raises the risk of gastric cancer is not known. Some human studies showed that the nicotine levels or other carcinogenic compounds in waterpipe is similar or higher than cigarette smoking.²⁸

Similar to the recent report from another population in Iran,¹⁹ we found a significant association between using opium (mainly smoking) and higher risk of gastric cancer. We were not able to obtain details of opium use to calculate the dose response effect, but the robust hazard ratio estimates after adjustment for other forms of smoking and lifestyle factors supports that the observed association was not due to confounding effects of other factors. The association of opium use with gastric cancer along with malignancies of the esophagus,¹⁴ bladder,¹⁶ lung¹⁷ and larynx¹⁸ warrants further awareness among medical and health professionals. Despite its illegal status, recent reports indicate a rising trend of opium use among the youth worldwide,^{21,29} which suggests higher numbers of opium-related cancer cases in the future. Association between opium use and human cancer have been discussed in different mechanisms. There is some evidence that have been showed opium could increase the ethylation of DNA through reduction of N-nitrosamines and N-nitrosodimethylamine. Also, it has been shown that opiates could work as cancer promotor by damage to human immune function and activating angiogenesis and tumour neovascularisation, and also increasing N-nitrosamines and related materials by changing their pharmacokinetics.²⁸

We try to control the effect of different confounders. We used Statistical adjustment for potential confounders availables such as age, sex, residence, education, intake of fruit and vegetables, cigarette smoking status and histological status. While in this cohort study, we have access to a large group of peoples who never used hookah or opium as the control group, it may be still some unmeasured confounders or modelling errors, although, there effect is not be considerable.²⁸

The role of diet in development of gastric cancer is of special interest. Among the broad range of dietary components and elements, daily intake of salt and fruit/vegetables have been investigated extensively in various populations at risk of gastric cancer. We showed an elevated cancer risk, as high as 4 times, in subject receiving more than 6 grams salt per day. This estimate of association is higher than an overall estimate reported in a recent meta-analysis by D'Elia et al,³⁰ perhaps due to different exposure definitions and data acquisition methods. The magnitude of association between salt intake and gastric cancer appears to be

confounded by several other factors; it is higher in the Japanese and in *H.pylori* infected populations with atrophic gastritis.¹⁰ Therefore, the higher estimates of cancer risk associated with salt intake in our cohort can be explained by the fact that all individuals were *H.pylori* infected and a large proportion of them had precancerous lesions (atrophic gastritis and intestinal metaplasia). A protective role for fresh fruit/vegetables against gastric cancer is still dubious^{31,32}; similarly, our finding did not show a significant inverse association between this factor and gastric cancer.

The association of gastric cancer with a number of macroscopic (endoscopic) and microscopic (histological) alterations has long been a point of interest for investigators. The pre-morbid histological state of gastric mucosa may predict cancer development later in life. A significant increase of cancer risk in individuals with either atrophic gastritis or intestinal metaplasia of gastric body on baseline examination in our cohort is consistent with previous observations.³³ These findings provide a mechanistic insight into gastric cancer development and highlight the stepwise nature of gastric cancer. Although some studies consider these precancerous lesions as risk factors (environmental or endogen), we are reluctant to do so, as they are neither environmental nor endogenous factors. In fact, precancerous lesions are intermediate steps in gastric carcinogenesis which arise as the result of a combination of exogenous and host factors. Therefore, intestinal metaplasia and atrophic gastritis may help determine subgroups of population who are at higher risk of cancer and thus need closer surveillance.

We showed that intestinal metaplasia was associated with high salt intake, hookah and opium use. Although cigarette smoking was not associated with any of the precancerous lesions in our study, associations with hookah use, as another form of tobacco smoking, is consistent with two previous studies on smoking and intestinal metaplasia.^{34,35} As ours is the first report to deal with the association between opium use and gastric intestinal metaplasia, more detailed investigations are needed to clarify the precise mechanism of opium carcinogenesis. The increased risk of intestinal metaplasia with high salt intake in our study indicates the carcinogenesis cascade might be facilitated by salt intake in earlier stages. This is consistent with the observation of Bergin et al who showed an induction of atrophic gastritis and intestinal metaplasia in Mongolian gerbils with salt-rich diets independently from *H.pylori* infection.³⁶

The association between a previously undiagnosed gastric ulcer, family history of gastric cancer and increased risk of gastric cancer risk later in life in our study is consistent with previous literature.^{37–41} Our results indicate that a vast majority of cancer cases might be prevented by elimination of modifiable risk factors without *H.pylori* eradication. From a prevention point of interest, manipulation of gastric cancer risk factors is feasible if limited to a few simple lifestyle factors. Our findings indicate that simple and low-cost strategies such as salt reduction and smoking cessation would lower gastric cancer incidence and overall mortality. Further studies are required to corroborate the influence of hookah and opium on gastric cancer incidence and thus contribute to designing efficient prevention strategies.

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References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010; 127:2893–917. [PubMed: 21351269]
2. Parkin DM, Ferlay J, Curado MP, Bray F, Edwards B, Shin HR, Forman D. Fifty years of cancer incidence: CI5 I-IX. *Int J Cancer*. 2010; 127:918–27.
3. Sadjadi A, Nouraie M, Mohagheghi MA, Mousavi-Jarrahi A, Malekezadeh R, Parkin DM. Cancer occurrence in Iran in 2002, an international perspective. *Asian Pac J Cancer Prev*. 2005; 6:359–63. [PubMed: 16236000]
4. Kolahdoozan S, Sadjadi A, Radmard AR, Khademi H. Five common cancers in Iran. *Arch Iran Med*. 2010; 13:143–6. [PubMed: 20187669]
5. Babaei M, Jaafarzadeh H, Sadjadi AR, Samadi F, Yazdanbod A, Fallah M, Aghlmandi A, Ramazani R, Haukka J, Hekmat SH, Didevar R, Shokoohi B, et al. Cancer Incidence and Mortality in Ardabil: Report of an Ongoing Population-Based Cancer Registry in Iran, 2004–2006. *Iranian Journal of Public Health*. 2009; 38:35–45.
6. Sadjadi A, Malekzadeh R, Derakhshan MH, Sepehr A, Nouraie M, Sotoudeh M, Yazdanbod A, Shokoohi B, Mashayekhi A, Arshi S, Majidpour A, Babaei M, et al. Cancer occurrence in Ardabil: results of a population-based cancer registry from Iran. *Int J Cancer*. 2003; 107:113–8. [PubMed: 12925965]
7. Roshandel G, Sadjadi A, Aarabi M, Keshtkar A, Sedaghat SM, Nouraie SM, Semnani S, Malekzadeh R. Cancer incidence in Golestan Province: report of an ongoing population-based cancer registry in Iran between 2004 and 2008. *Arch Iran Med*. 2012; 15:196–200. [PubMed: 22424034]
8. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res*. 1992; 52:6735–40. [PubMed: 1458460]
9. Barreto-Zuñiga R, Maruyama M, Kato Y, Aizu K, Ohta H, Takekoshi T, Bernal SF. Significance of *Helicobacter pylori* infection as a risk factor in gastric cancer: serological and histological studies. *J Gastroenterol*. 1997; 32:289–94. [PubMed: 9213239]
10. Shikata K, Kiyohara Y, Kubo M, Yonemoto K, Ninomiya T, Shirota T, Tanizaki Y, Doi Y, Tanaka K, Oishi Y, Matsumoto T, Iida M. A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. *Int J Cancer*. 2006; 119:196–201. [PubMed: 16450397]
11. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition, physical activity and the prevention of cancer: a global perspective. Washington DC: AICR; 2007.
12. Shikata K, Ooi DY, Yonemoto K, Arima H, Ninomiya T, Kubo M, Tanizaki Y, Matsumoto T, Iida M, Kiyohara Y. Population-based prospective study of the combined influence of cigarette smoking and *helicobacter pylori* infection on gastric cancer incidence, The hisayama study. *Am J Epidemiol*. 2008; 168:1409–1415. [PubMed: 18945691]
13. 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 Causes Control*. 2008; 19:689. [PubMed: 18293090]
14. Friesen M, O'Neill IK, Malaveille C, Garren L, Hautefeuille A, Bartsch H. 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; 8:1423–32. [PubMed: 3652380]

15. Nasrollahzadeh D, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet CC, Shakeri R, Pourshams A, Marjani HA, Nouraie M, Khatibian M, Semnani S, Ye W, Boffetta P, Dawsey SM, Malekzadeh R. 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]
16. 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]
17. 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*. 2013; 85:112–8. [PubMed: 22759984]
18. Mousavi MR, Damghani MA, Haghdoust AA, Khamesipour A. Opium and risk of laryngeal cancer. *Laryngoscope*. 2003; 113:1939–43. [PubMed: 14603052]
19. Shakeri R, Malekzadeh R, Etemadi A, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, Islami F, Pourshams A, Pawlita M, Boffetta P, Dawsey SM, Abnet CC, Kamangar F. Opium: An emerging risk factor for gastric adenocarcinoma. *Int J Cancer*. 2013; doi: 10.1002/ijc.28018
20. Sutfin EL, McCoy TP, Reboussin BA, Wagoner KG, Spangler J, Wolfson M. Prevalence and correlates of waterpipe tobacco smoking by college students in North Carolina. *Drug Alcohol Depend*. 2011; 115:131–6. [PubMed: 21353750]
21. UNODC. World Drug Report_2011. United Nations Office on Drugs and Crime; 2011.
22. TobReg Wsgotpr. Waterpipe tobacco smoking: Health effects, research needs and recommended actions by regulators. World Health Organization (WHO); 2005.
23. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol*. 1996; 20:1161–81. [PubMed: 8827022]
24. Khademi H, Etemadi A, Kamangar F, Nouraie M, Shakeri R, Abaie B, Pourshams A, Bagheri M, Hooshyar A, Islami F, Abnet CC, Pharoah P, Brennan P, Boffetta P, Dawsey SM, Malekzadeh R. Verbal autopsy: reliability and validity estimates for causes of death in the Golestan Cohort Study in Iran. *PLoS One*. 2010; 5:e11183. [PubMed: 20567597]
25. Inoue M, Sawada N, Matsuda T, Iwasaki M, Sasazuki S, Shimazu T, Shibuya K, Tsugane S. Attributable causes of cancer in Japan in 2005--systematic assessment to estimate current burden of cancer attributable to known preventable risk factors in Japan. *Ann Oncol*. 2012; 23:1362–9. [PubMed: 22048150]
26. Derakhshan MH, Malekzadeh R, Watabe H, Yazdanbod A, Fyfe V, Kazemi A, Rakhshani N, Didevar R, Sotoudeh M, Zolfeghari AA, McColl KE. Combination of gastric atrophy, reflux symptoms and histological subtype indicates two distinct aetiologies of gastric cardia cancer. *Gut*. 2008; 57:298–305. [PubMed: 17965056]
27. 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]
28. Khademi H, Malekzadeh R, Pourshams A, Jafari E, Salahi R, Semnani S, Abaie B, Islami F, Nasser-Moghaddam S, Etemadi A, Byrnes G, Abnet CC, Dawsey SM, Day NE, Pharoah PD, Boffetta P, Brennan P, Kamangar F. Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50,000 adults in Iran. *BMJ*. 2012; 344:e2502. [PubMed: 22511302]
29. Sadeghi-Bazargani H, Jafarzadeh H, Fallah M, Hekmat S, Bashiri J, Hosseingolizadeh Gh, Soltanmohammadzadeh MS, Mortezaazadeh A, Shaker A, Danehzan M, Zohouri A, Khosravi O, Nasimidoust R, Malekpour N, Kharazmi E, Babaei M, Nadirmohammadi M, Mashhadi-Abdollahi H. Risk factor investigation for cardiovascular health through WHO STEPS approach in Ardabil, Iran. *Vasc Health Risk Manag*. 2011; 7:417–24. [PubMed: 21796256]
30. D'Elia L, Rossi G, Ippolito R, Cappuccio FP, Strazzullo P. Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies. *Clin Nutr*. 2012; 31:489–98. [PubMed: 22296873]
31. Lunet N, Lacerda-Vieira A, Barros H. Fruit and vegetables consumption and gastric cancer: a systematic review and meta-analysis of cohort studies. *Nutr Cancer*. 2005; 53:1–10. [PubMed: 16351501]

32. Steevens J, Schouten LJ, Goldbohm RA, van den Brandt PA. Vegetables and fruits consumption and risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. *Int J Cancer*. 2011; 129:2681–93. [PubMed: 21960262]
33. de Vries AC, van Grieken NC, Looman CW, Casparie MK, de Vries E, Meijer GA, Kuipers EJ. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. *Gastroenterology*. 2008; 134:945–52. [PubMed: 18395075]
34. Russo A, Maconi G, Spinelli P, Felice GD, Eboli M, Andreola S, Ravagnani F, Settesoldi D, Ferrari D, Lombardo C, Bertario L. Effect of lifestyle, smoking, and diet on development of intestinal metaplasia in *H. pylori*-positive subjects. *Am J Gastroenterol*. 2001; 96:1402–8. [PubMed: 11374674]
35. Peleteiro B, Lunet N, Figueiredo C, Carneiro F, David L, Barros H. Smoking, *Helicobacter pylori* virulence, and type of intestinal metaplasia in Portuguese males. *Cancer Epidemiol Biomarkers Prev*. 2007; 16:322–6. [PubMed: 17301266]
36. Bergin IL, Sheppard BJ, Fox JG. *Helicobacter pylori* infection and high dietary salt independently induce atrophic gastritis and intestinal metaplasia in commercially available outbred Mongolian gerbils. *Dig Dis Sci*. 2003; 48:475–85. [PubMed: 12757158]
37. Hansson LE, Nyren O, Hsing AW, Bergstrom R, Josefsson S, Chow WH, Fraumeni JF Jr, Adami HO. The risk of stomach cancer in patients with gastric or duodenal ulcer disease. *N Engl J Med*. 1996; 335:242–9. [PubMed: 8657240]
38. Take S, Mizuno M, Ishiki K, Nagahara Y, Yoshida T, Yokota K, Oguma K, Okada H, Shiratori Y. The effect of eradicating *helicobacter pylori* on the development of gastric cancer in patients with peptic ulcer disease. *Am J Gastroenterol*. 2005; 100:1037–42. [PubMed: 15842576]
39. Lu PJ, Hsu PI, Chen CH, Hsiao M, Chang WC, Tseng HH, Lin KH, Chuah SK, Chen HC. Gastric juice acidity in upper gastrointestinal diseases. *World J Gastroenterol*. 2010; 16:5496–501. [PubMed: 21086570]
40. Hemminki K, Sundquist J, Ji J. Familial risk for gastric carcinoma: an updated study from Sweden. *Br J Cancer*. 2007; 96:1272–7. [PubMed: 17406355]
41. Yaghoobi M, Bijarchi R, Narod SA. Family history and the risk of gastric cancer. *Br J Cancer*. 2010; 102:237–42. [PubMed: 19888225]

What's New?

Hookah and opium are associated with many malignancies. This cohort study is the first to investigate associations between hookah/opium and gastric precancerous lesions and gastric cancer in *H.pylori* infected subjects. Both hookah/opium were strongly associated with not only gastric cancer but also atrophic gastritis and intestinal metaplasia. Furthermore, a major fraction of gastric cancers were shown to be attributed to modifiable risk factors: high salt intake, smoking (cigarette, hookah, opium) and insufficient fruit/vegetable intake.

Table 1
Main baseline characteristics of participants in the cohort of *H. pylori* infected subjects

Baseline Feature		Endoscopic finding					Histological finding			
	Total (n=928)	Normal (n=29)	Gastritis (n=847)	DU (n=18)	GU (n=28)	DU & GU (n=6)	Normal (n=10)	CG (n=417)	AG (n=372)	IM (n=129)
Male (%)	49.1	42.3	43.2	72.2	57.1	66.7	55.6	51.3	46.8	56.2
Mean age (SD), years	53.1 (9.9)	47.3 (9.2)	51.7 (9.5)	56.3 (10.7)	52.3 (9.1)	53.2 (10.1)	56.7 (13.2)	51.2 (9.4)	53.5 (10.0)	58.0 (9.3)
Family history of gastric cancer (%)	20.7	23.1	20.9	22.2	53.6	33.3	11.1	17.5	20.9	30.5
Cigarette smoking (%)	39.1	38.5	39.7	61.1	46.4	50.0	33.3	39.1	37.4	48.4
Hookah smoking (%)	8.0	0	8.9	5.6	14.3	0	0	3.2	5.8	11.7
Opium use (%)	1.9	6.8	1.6	11.1	5.1	16.6	0	1.1	1.3	3.3
Alcohol use (%)	4.7	3.8	4.4	0	4.5	0	0	4.0	4.2	7.8
Low fruit/veg. intake < 400 gr/day, (%)	72.2	69.4	67.6	82.1	94.4	83.4	68.9	70.1	74.5	76.7
High salt intake, > 6 gr/day, (%)	81.6	81.1	79.8	82.1	88.9	100	81.1	80.1	79.7	83.4
No school or elementary school (%)	75.2	57.7	74.9	83.3	67.9	66.7	66.7	69.3	78.9	82.8

Normal histology: No infiltration by polymorphonuclear or mononuclear leukocytes, no atrophy, and no IM. CG: chronic gastritis, AG: atrophic gastritis (grade 1 or more) in at least one site of biopsy from either antrum or corpus, IM: intestinal metaplasia (grade 1 or more) in at least one site of biopsy from either antrum or corpus, DU: duodenal ulcer, GU: gastric ulcer.

Table 2

Incidence rate of gastric cancer (per 1,000 person-years) associated with risk factors recorded on baseline evaluation in the cohort of *H. pylori* infected subjects

Risk factor	Cohort (Person-Years)	Incident gastric cancer (n)	Incidence Rate (n/1000 PY)	P Value
Family history of gastric cancer (+)	1832.7	23	12.5	0.0001
Family history of gastric cancer (–)	7564.3	13	1.7	
Cigarette smoking (+)	3601.3	28	7.8	0.0001
Cigarette smoking (–)	5790.0	8	1.4	
Hookah smoking (+)	709.6	12	16.9	0.0001
Hookah smoking (–)	8681.5	24	2.7	
Opium use (+)	165.0	4	24.3	0.004
Opium use (–)	9226	32	3.5	
Fruit/veg. intake < 400 gr/day	6424.6	29	4.6	0.343
Fruit/veg. intake ≥ 400 gr/day	2972.5	7	2.3	
Salt intake > 6 gr/day	7640.3	34	4.5	0.025
Salt intake ≤ 6 gr/day	1757.0	2	1.1	
Gastric ulcer (+)	234.7	7	29.8	0.0001
Gastric ulcer (–)	9162.4	29	3.2	
Duodenal ulcer (+)	186.1	1	5.4	0.513
Duodenal ulcer (–)	9211	35	3.8	
Atrophic gastritis (+)	3708.3	28	7.6	0.0001
Atrophic gastritis (–)	5688.8	8	1.4	
Intestinal metaplasia (+)	1284.0	25	19.5	0.0001
Intestinal metaplasia (–)	8113.2	11	1.4	

Table 3

Association between baseline gastric precancerous lesions and lifestyle risk factors adjusted to either age or all variables in the cohort of *H. pylori* infected subjects

	Antral Atrophic Gastritis		Antral Intestinal Metaplasia		Body Atrophic Gastritis		Body Intestinal Metaplasia	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age adjusted								
Cigarette smoking	0.89 (0.7–1.2)	0.379	1.32 (0.9–2.0)	0.174	1.23 (0.9–1.6)	0.163	1.29 (0.8–2.1)	0.328
Hookah smoking	0.63 (0.4–1.04)	0.072	1.87 (1.01–3.5)	0.046	0.66 (0.4–1.2)	0.152	1.30 (0.6–3.0)	0.532
Opium use	1.29 (0.5–3.3)	0.599	3.61 (1.3–9.7)	0.011	2.47 (1.0–6.4)	0.063	6.84 (2.5–18.8)	0.001
Salt intake >6 gr/day	1.02 (0.7–1.4)	0.893	2.62 (1.4–5.0)	0.004	0.83 (0.6–1.2)	0.431	1.31 (0.7–2.6)	0.431
Fruit/Veg. intake < 400 gr/day	1.12 (0.8–1.5)	0.460	0.74 (0.5–1.1)	0.173	1.66 (1.2–2.3)	0.003	1.91 (1.0–3.7)	0.058
Multivariable adjusted*								
Hookah smoking	-	-	1.69 (0.9–3.2)	0.106	-	-	-	-
Opium use	-	-	3.29 (1.2–9.1)	0.022	-	-	7.34 (2.5–21.5)	0.001
Salt intake >6 gr/day	-	-	2.55 (1.3–4.9)	0.006	-	-	-	-
Fruit/Veg. intake < 400 gr/day	-	-	-	-	1.69 (1.2–2.4)	0.003	2.08 (1.05–4.1)	0.036

Risk of gastric cancer associated with modifiable lifestyle, gender, and family history of gastric cancer, adjusted to either age or all variables in the cohort of *H. pylori* infected subjects

Table 4

Factor	Age adjusted			Multivariable adjusted*		
	HR	95%CI	P value	HR	95%CI	P Value
Gender	Female	1	-	-	-	-
	Male	1.33	0.69 – 2.59	0.398	-	-
Family history of cancer	No	1	-	1	-	-
	Yes	7.54	3.82 – 14.90	0.0001	5.70	2.80–11.60
Cigarette smoking	No	1	-	1	-	-
	Yes	5.35	2.44 – 11.73	0.0001	3.21	1.37–7.48
Hookah smoking	No	1	-	1	-	0.001
	Yes	5.65	2.82–11.32	0.0001	3.44	1.66–7.11
Opium use	No	1	-	1	-	-0.007
	Yes	4.6	1.6–13.3	0.004	3.24	1.37–7.66
Alcohol use	No	1	-	-	-	-
	Yes	1.75	0.42 – 7.32	0.444	-	-
Fruit/veg. intake <400 gr/day	No	1	-	-	-	-
	Yes	1.71	0.62–3.22	0.410	-	-
Salt intake >6 gr/day	No	1	-	1	-	-
	Yes	5.09	1.22 – 21.23	0.026	4.88	1.17 – 20.34

HR: hazard ratio, CI: confidence interval

* Adjusted to age and all other variables in the table

Risk of gastric cancer associated with endoscopic and histological parameters adjusted to either age or all variables in the cohort of *H. pylori* infected subjects

Table 5

Factors	Age adjusted			Multivariable adjusted		
	HR	95% CI	P value	HR	95% CI	P value
Gastric ulcer	No	1	-	1	-	-
	Yes	11.91	5.13–27.67	<0.001	9.01	3.27–24.80
Duodenal Ulcer	No	1	-	-	-	-
	Yes	1.03	0.14–7.61	0.970	-	-
Antral Atrophic Gastritis	No	1	-	<0.001 [#]	1	-
	Mild	1.92	0.88–4.22		0.95	0.38–2.35
	Moderate	4.55	1.86–11.17		0.85	0.25–2.93
	Marked	8.20	2.31–29.10		0.52	0.06–4.44
Antral intestinal metaplasia	No	1	-	<0.001 [#]	-	-
	Mild	4.17	1.91–9.09		1.16	0.41–3.21
	Moderate	10.79	4.15–27.90		1.37	0.35–5.34
	Marked	10.67	2.46–46.11		1.27	0.12–13.99
Body Atrophic Gastritis	No	1	-	<0.001 [#]	1	-
	Mild	3.04	1.19–7.74		2.08	0.74–5.80
	Moderate	10.27	4.36–24.19		3.60	1.14–11.34
	Marked	10.69	3.55–32.19		6.77	1.62–28.43
Body intestinal metaplasia	No	1	-	<0.001 [#]	1	-
	Mild	6.92	2.85–16.80		4.45	1.61–12.29
	Moderate	23.03	8.91–59.50		9.83	2.57–37.60
	Marked	18.23	6.71–49.54		10.97	2.53–47.48

HR: hazard ratio, CI: confidence interval.

* Adjusted to age and all above factors with significant association with age-adjusted model;

P Value for Trend
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Table 6

The fraction of gastric cancer attributable (AF) to preventable risk factors in the current study of *H.pylori* infected subjects

Factor	Population at risk	Case No.	AF % - (95% CI)
High salt intake (> 6gr/day)	757	34	70.64 (32.73 – 90.24)
Smoking (cigarette and hookah)	363	28	62.04 (47.21 – 75.13)
Opium use	18	4	8.32 (2.09 – 16.04)
Low intake of fruit/veg. (<400 gr/day)	670	29	31.52 (0.51 – 53.85)
High salt + Smoking + Low fruit/veg.	844	36	92.37 (81.38 – 97.92)
High salt + Smoking + Low fruit/veg. + opium use	845	36	93.00 (82.90 – 98.10)