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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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A recent study showed an association between hookah/opium use and gastric cancer but no study has investigated the relationship 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 ratios (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: 3.96/1,000 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.

Gastric cancer holds a special place among worldwide malignancies in terms of both mortality and incidence. 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 noncardia, 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 suggest a potential role for other lifestyle and genetic risk factors in the course of this malignancy.[2] Current knowledge on lifestyle and dietary factors of gastric cancer leaves no doubt about the role

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What's new?

Gastric cancer strikes Iranian men more often than any other cancer, and previous studies report a connection between gastric cancer and hookah, a traditional smoking device in the region. This study probed the factors associated with precancerous lesions and gastric cancer, including hookah and opium use. They found that both hookah and opium use increased the likelihood of developing cancer, as did high salt intake and cigarette smoking.

of well-established factors including excess salt intake,[10] low intake of fresh fruit/vegetable[11] and smoking.[12,13]

Several studies have reported associations between opium and different malignancies, namely esophagus,[14,15] bladder,[16] lung[17] and larynx.[18] A recent study 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 reportedly growing among younger populations of Western countries.[20] Although largely believed by the public to be less harmful than cigarettes, the report by Shakeri *et al.* suggests hookah's association with gastric cancer in Iran.[19] On the basis of the growing epidemiological evidence on the role of opium and hookah, and lack of mechanistic studies on the topic, the World Health Organization has encouraged further research on hookah/opium association with malignancies, including gastric cancer.[21,22]

We aimed to investigate the factors associated with gastric caner and precancerous lesions, including hookah and opium as neglected risk factors, in a follow-up study of *H. pylori*-infected subjects. As our study is one of the few investigations with baseline histological information, we could evaluate the association between precancerous lesions (atrophic gastritis and intestinal metaplasia) and 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, AF).

Material and Methods
Study population
This population-based follow-up study took place in Ardabil province, Northwest Iran. Participants were chosen through random selection from permanent residents of urban and rural areas in Ardabil (province capital) and Meshkinshahr townships, who were aged 40 years or more. The exclusion criteria were participant's refusal, known gastrointestinal, cardiac or respiratory disease and pregnancy. Mild dyspepsia symptoms without a definite prescription by a physician were not an exclusion criterion. 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 our 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 and data handling
Initially, investigators recorded all data pertaining to potential risk factors using validated questionnaires. 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 g salt/day, and low fruit/vegetable intake was defined as eating less than 400 g/day. The subjects subsequently underwent upper gastrointestinal endoscopy and at least one biopsy was taken from incisura angularis, two from lesser curvature (one from halfway between incisura and cardia and one from pre-pyloric area) and two from greater curvature (one from fundus and one from antrum). 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
The 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. National and local cancer and death registries contributed to the follow-up process. Authors regularly searched the relevant cancer and death registries to extract the time of gastric cancer events. Trained physicians directly contacted all participants (or their next of kin) for whom no records were found in above registries to determine their health status.

Cancer diagnoses
Cancer diagnoses were based on histology of specimen collected on endoscopy or surgery. If unavailable, alternative means were used, namely, radiology reports, physician reports (endoscopy and clinical diagnosis) and 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 precancerous lesions as main outcome were investigated using logistic regression models; the odds ratios (ORs) and 95% confidence intervals (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 ratios (HRs) and 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 AF for modifiable risk factors [smoking (including hookah), opium, high salt intake and low fruit/vegetable consumption] was calculated using Miettinen's formula.[24]

$$AF_P = P(RR_a - 1)/RR_a$$

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[24]

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

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.

All tests throughout the article were two-sided, and *p* values < 0.05 were considered 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 of Tehran University of Medical Sciences.

Results
Nine hundred and twenty-eight participants included in our 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 3.96/1,000 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 six (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 cell 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

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

Baseline feature	Total (n = 928)	Endoscopic finding					Histological finding			
		Normal (n = 29)	Gastritis (n = 847)	DU (n = 18)	GU (n = 28)	DU and 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	5.6	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 g/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 g/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

Abbreviations: 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*/1,000 person-years)	*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 (−)	9,226	32	3.5	
Fruit/veg. intake < 400 g/day	6424.6	29	4.6	0.343
Fruit/veg. intake ≥ 400 g/day	2972.5	7	2.3	
Salt intake > 6 g/day	7640.3	34	4.5	0.025
Salt intake ≤ 6 g/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 (−)	9,211	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	

129 (13.9%) of participants, respectively. Only ten (1.08%) people had nonspecific minimal changes (normal histology) and no dysplasia cases were found in our study.

As detailed in Table 2, the incidence rate of cancer in those with positive family history was 12.5/1,000 person-years, whereas it was as low as 1.7/1,000 person-years in other participants. Among lifestyle factors, smoking tobacco increased the incidence rate of cancer significantly (7.8 *vs.* 1.4/1,000 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.* 3.5/1,000 person-years). High salt intake (>6 g/day) increased the incidence rate of cancer significantly (4.5 *vs.* 1.1/1,000 person-years), but the effect of lower intake of fruit/vegetable on cancer risk was not statistically considerable. Among endoscopic findings, active gastric ulcer was associated with an increased cancer incidence: 29.8 *vs.* 3.2/1,000 person-years. Having either atrophic gastritis (7.6 *vs.* 1.4/1,000 person-years) or intestinal metaplasia (19.5 *vs.* 1.4/1,000 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. 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/vegetable 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/vegetable 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 (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/vegetable were not associated with a higher risk of cancer.

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 g/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 g/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[1]								
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 g/day	–	–	2.55 (1.3–4.9)	0.006	–	–	–	–
Fruit/veg. intake < 400 g/day	–	–	–	–	1.69 (1.2–2.4)	0.003	2.08 (1.05–4.1)	0.036

[1]Adjusted to age and all other variables in the table.

Table 4. 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

		Age adjusted			Multivariable adjusted[1]		
Factor		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	0.0001
Cigarette smoking	No	1	–	–	1	–	–
	Yes	5.35	2.44–11.73	0.0001	3.21	1.37–7.48	0.007
Hookah smoking	No	1	–		1	–	
	Yes	5.65	2.82–11.32	0.0001	3.44	1.66–7.11	0.001
Opium use	No	1			1	–	–
	Yes	4.6	1.6–13.3	0.004	3.24	1.37–7.66	0.007
Alcohol use	No	1	–		–	–	–
	Yes	1.75	0.42–7.32	0.444	–	–	–
Fruit/veg. intake <400 g/day	No	1	–	–	–	–	–
	Yes	1.71	0.62–3.22	0.410	–	–	–
Salt intake >6 g/day	No	1	–	–	1	–	–
	Yes	5.09	1.22–21.23	0.026	4.88	1.17–20.34	0.030

[1]Adjusted to age and all other variables in the table.
Abbreviations: HR: hazard ratio; CI: confidence interval.

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 gastri-tis 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).

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Table 5. 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

Factors		Age adjusted			Multivariable adjusted[1]		
		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	<0.001
Duodenal ulcer	No	1	–	–	–	–	–
	Yes	1.03	0.14–7.61	0.970	–	–	–
Antral atrophic gastritis	No	1	–	<0.001[#]	1	–	0.946[#]
	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[#]	–	–	0.975[#]
	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	–	0.036[#]
	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	–	0.001[#]
	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	

[1]Adjusted to age and all above factors with significant association with age-adjusted model. #*p* Value for trend.
Abbreviations: HR: hazard ratio; CI: confidence interval.

Table 6. The fraction of gastric cancer attributable (AF) to preventable risk factors in our study of *H. pylori*-infected subjects

Factor	Population at risk	Case no.	AF % (95% CI)
High salt intake (>6 g/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 g/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)

Furthermore, in analyses by histological subtypes of adenocarcinoma (intestinal *versus* diffuse type), the difference between groups was not significant as only a few cases had the diffuse subtype (nine of 36 cases; data not shown).

Finally, we calculated the 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/vegetable was 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

Our 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 10-year follow-up, equal to 9,096 person-years, discovered 36 cases of gastric cancer (incidence: 3.96/1,000 person years). Both hookah and opium were found to be strongly associated with gastric

cancer, as well as atrophic gastritis and intestinal metaplasia. Additionally, 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, ~93% of gastric cancers were theoretically attributable to the joint effects of high salt intake, low fruit intake, smoking (any type) and opium. Our 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. 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.[25,26] Hookah is gaining popularity among the youth, partly because of the common belief that it is safer than cigarettes. Nevertheless, we found a threefold higher risk of gastric cancer. An association between hookah smoking and gastric cancer has also been shown in another study.[19] The mechanism by which hookah raises the risk of gastric cancer is not known completely, although three recent studies demonstrated that hookah smoke contains a broad range of carcinogenic and toxic substances including nitrosamines, polycyclic aromatic hydrocarbons, primary aromatic amines and carbon monoxide and various furanic compounds such as 5-(hydroxymethyl)-2-furaldehyde.[27–29]

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 support that the confounding effects of other factors are less likely. Nevertheless, presence of unknown confounders, particularly those with carcinogenic pathways shared with smoking, cannot be ignored.

The association of opium with gastric cancer along with malignancies of the esophagus,[14] bladder,[16] lung[17] and larynx[18] 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,[21,30] which suggests higher numbers of opium-related cancer cases in the future.

The role of diet in the development of gastric cancer is of special interest. Among the broad range of dietary components and elements, daily intake of salt and fruit/vegetable has been investigated extensively in various populations. We showed an elevated cancer risk, as high as four times, in subjects receiving more than 6 g salt per day. This estimate of association is higher than an overall estimate reported in a recent meta-analysis by D'Elia *et al.*[31] perhaps because of 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/vegetable against gastric cancer is still dubious[32,33]; 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 premorbid 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.[34] 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 endogenous), 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. 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.[35,36] As ours is the first report to deal with the association between opium 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 that 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.[37]

The association between a previously undiagnosed gastric ulcer and an increased risk of gastric cancer risk later in life in our study, and lack of such an association for duodenal ulcer, is consistent with previous literature.[38,39] This may be explained by the gastric hypersecretory state in patients with duodenal ulcer and hypochlorhydria in those with gastric ulcer; hypochlorhydria is a common mechanistic link between gastric ulcer and gastric cancer.[40]

In conclusion, our study could suggest a much simpler and more effective strategy for prevention of gastric cancer in *H. pylori*-infected subjects in high incidence areas such as Ardabil where the majority of people acquire *H. pylori* infection during neonatal period and develop some degrees of precancerous lesions in middle age. Our results indicate that

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many cancer cases might be prevented by elimination of modifiable risk factors without *H. pylori* eradication. In fact, gastric cancer is a multifactorial disease, mainly developing in an inflammatory background induced by *H. pylori* infection, with many lifestyle factors contributing to its progress. For the purpose of prevention, 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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