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Title Page

Opium Use and the Risk of Head and Neck Squamous Cell Carcinoma

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Abbreviations list:

DMFT: Decayed, Missing, and Filled Teeth Index

HNSCC: Head and Neck Squamous Cell Carcinoma

HPV: *Human Papillomavirus*

IROPICAN: Iran Opium and Cancer Study

ORs: Odds Ratios

95% CI: 95% Confidence Intervals

Novelty Impact:

The carcinogenicity of opium use has been studied for many organs while head and neck cancer evidence is limited. Using more than 600 cases of head and neck squamous cell carcinoma and about 3000 controls from the highest prevalent country of opium use showed the risk of the cancer could be increased more than three times in regular opium users than non-users. The risk was even more intensified for laryngeal cancer.

Abstract

Scant evidence exists to support the association of opium use with head and neck cancer, limited to the larynx and oral cavity. In a multicenter case-control study -Iran Opium and Cancer study (IROPICAN), we recruited 633 cases of head and neck squamous cell carcinoma (HNSCC) (254 lip and oral cavity, 54 pharynx, 327 larynx, and 28 other sub-sites within the head and neck) and 3065 frequency-matched controls from April 2016 to April 2019. Odds ratios (ORs) for opium use and 95% confidence intervals (95% CIs) were obtained using mixed-effects logistic regression because of heterogeneity amongst centers. The adjusted OR (95% CI) for regular opium use was 3.76 (2.96 to 4.79) for all HNSCC combined. Strong dose-response effects were observed by frequency or amount of use, and duration of use. Regular opium uses significantly increased the risk of HNSCC of the pharynx, larynx, and other sub-sites within the head and neck with OR (95% CI) of 2.90 (1.40 to 6.02), 6.55 (4.69 to 9.13), and 5.95 (2.41 to 14.71), respectively. The observed associations were significant even among never tobacco smokers (including cigarette and water-pipe smoking). Moreover, by the multiplicative interaction scale, the effect of opium use could be varied by cigarette smoking on HNSCC, 8.16 (6.20 to 10.74). For the first time, the current study showed opium users have an increased risk of several anatomic sub-sites of HNSCC.

Introduction

On a global scale, in 2018, an estimated 834,860 individuals developed new cancers of the lip, oral cavity, pharynx, and larynx, of whom 431,131 died due to these cancers [1]. A variety of etiological factors have been identified for head and neck cancers, including tobacco smoking, alcohol drinking, chewing betel quid, consumption of nitrosamine-rich foods, and infection like *Human Papillomavirus* (HPV) [1].

Opium use is originated from the South Asian countries and the East Mediterranean including Iran. Although opium use is legally prohibited in Iran, it is the most commonly used drug [2]. Using opium has been identified as a risk factor for several cancers like cancers of bladder and lung [3-5]. However, there is very little data on the association of opium use and cancers of head and neck cancers.

A few case-control studies have found strong associations between the use of opium and the risk of laryngeal cancer [6-10]. The risk of supraglottic laryngeal cancer was also associated with a prescription intravenous opioid in a case-control study [11]. Likewise, preliminary results from the Golestan cohort study also showed an increased risk of death due to laryngeal cancer in opium users [12]. Consistent with these findings, an ecological study in Iran showed a correlation between higher opium use and higher incidence rates of laryngeal cancer [13]. On the other hand, recent data from the national population-based cancer registry in Iran showed that the highest incidence rate of laryngeal cancer was reported from Kerman province [14], whereas the prevalence of opium consumption was higher than other regions [15].

There were, however, serious limitations to previous studies of opium and laryngeal cancer. The earliest studies were conducted in the 1980s [6, 7], when the results were not typically adjusted for important confounding factors, such as tobacco smoking. Sample sizes were small-less than fifty cases-in some other studies. Furthermore, most previous studies were not primarily designed to study the

effect of opium use on cancer, and as such, case and control selection and data collection methods were not optimal for this purpose.

We designed the Iran Opium and Cancer study (IROPICAN) to study the association of opium use and some types of cancers among that opium use could be a possible and plausible risk factor, including cancers of the lip, oral cavity, pharynx, and larynx. To overcome the limitations of the previous studies, we enrolled over 600 such cancer cases and 3000 controls in this study and optimized data collection and control selection methods during pilot studies [16]. The present report summarizes the findings of the IROPICAN study for all HNSCC cancers combined and cancers of the lip, oral cavity, pharynx, and larynx, separately.

Methods

Data come from the IROPICAN study, a large multicenter case-control study conducted in 10 different provinces. These provinces were selected because the prevalence of opium use is relatively high in these regions.

Case selection

Cases were incident head and neck squamous cell carcinomas (HNSCC) during April 2016 and April 2019, who referred to cancer care centers in the provinces. A team of trained researchers actively reviewed the admission and treatment notes of relevant wards (e.g. surgical oncology wards) to identify potentially eligible HNSCC patients. The pathology reports were reviewed by the focal researchers and if needed they consulted clinicians to ensure the diagnosis. All head and neck cancer pathology reports that were not squamous cell types were excluded. HNSCC cases were further categorized by tumor sites according to the *International Classification of Diseases, Tenth Edition* [17].We included cancers of lip (codes C00.0-C00.6, C00.8, and C00.9), oral cavity (codes C01.9, C02.0-C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0- C05.2, C05.8, C05.9, C06.0-C06.2, C06.8,

C06.8, and C06.9), salivary glands (codes C07.9, C08.0, C08.1, C08.08, and C08.9), tonsil (codes C09.0, C09.1, C09.8, and C09.9), oropharynx (codes C10.0-10.4, C10.8, and C10.9), nasopharynx (codes C11.0-C11.3, C11.8, and C11.09), hypopharynx (codes C13.0-C13.2, C13.8, and C13.9), other and ill-defined sites in lip, oral cavity and pharynx (codes C14.0, C14.2, and C14.8), nasal cavity and middle ear (codes C30.0 and C30.1), sinuses (codes C12.9, C31.0-C31.3, C31.8, C31.9), larynx (codes C32.0-C32.3, C32.8, and C32.9), other and ill-defined sites (code C76.0), and head and neck cancers were overlapping or unspecified[17]. For analysis, the codes categorized to lip and oral cavity including codes C00-C08 and C14, pharynx codes C09-C11 and C13, larynx codes C32, and other sub-sites within head and neck codes C12, C31, C32, and C76. As only squamous cell carcinoma of head and neck was included, IROPICAN clinical consultant-head and neck surgeon- recommended combining the codes of other sub-sites (28 cases).

Control selection

We selected at least four controls for each case, frequency-matched by age, sex, and place of residence. Potential controls were hospital visitors who were relatives or friends of hospitalized patients either in non-oncology wards or who visited the hospital for any reason other than receiving treatment concurrently [16]. To reduce selection bias emergency rooms and maternity wards were excluded for control recruitment because the referral pattern of the wards was more likely dependent on the residential area of residences e.g. accident injured persons referred to the closest EMR, furthermore, drug and alcohol users increase car collision rate [18, 19]. The controls were recruited in the same hospitals as the cases or in comparable referral hospitals of the catchment area. To be eligible, the controls had to be also free of any history of cancer reported by themselves.

We chose controls from among hospital visitors every day by a predefined protocol, previously we found that the prevalence of self-reported regular opioid use among hospital visitors was comparable

to the general population[16]. Moreover, a high level of sensitivity (77%) for self-reporting of opium use among hospital visitor controls supported the use of hospital visitors as controls [16].

Data collection

A team of trained interviewers administered a structured questionnaire to both cases and controls. This questionnaire included detailed data on demographics, history of opium and tobacco use, history of alcohol drinking, oral health, and socioeconomic status. The same team of trained interviewers also conducted physical exams including standardized measurements of height, weight, and blood pressure (both cases and controls). In each center, an assigned nurse collected blood and saliva samples using a predefined protocol.

Opium exposure measurement

We collected a detailed history of opium use including the age of starting and ending use, frequency of use, the typical amount of use, types of opiates, and routes of administration. In Iran, opium is used in various forms, including Teriak (crude opium), Sukhteh (remnants of smoked opium or dross), and Shireh (opium juice, an opium product usually made by boiling Teriak or Sukhteh with water, filtering the mixture several times, and then evaporating the filtrate) [20]. Because very few numbers of Sukhteh users (four users), we merged Sukhteh and Teriak. Regular opium user was defined as using opium at least once a week for at least six consecutive months. Route of opium use was also inquired since all forms of opium can be used via smoking and oral ingestion.

A measure of cumulative opium use in a lifetime was defined as the sum of the amount of opium use (gram per day) multiplied by the amount of use in each duration of opium use in a lifetime (gram-year). Another approach to explore dose-response was the multiplication of frequency of use and duration of that period of opium use (frequency-year) [21]. The other metric of opium is the average intensity of opium use. The average intensity of opium was calculated by dividing the cumulative

opium use to the duration of that period. All of the measures were categorized into three groups by the tertile of the control group.

Reverse causality is an important concern for the association of opium use and any cancer, since the patients may start using opium to alleviate their pain which could be a prodromal symptom of the subsequently diagnosed cancer. Thus, we disregarded opium use in those who started three years before diagnosis. Consequently, six patients were categorized as the non-opium user to reduce reverse causation in all analyses and tables.

In the validation study, we found that current opium use had limited sensitivity when tested against morphine in urine [16]. Hence, it is plausible that the regular use of opium subject to more non-differential misclassification (information bias). To overcome information bias -underreporting of opium use- we calculated ORs for a range of 0.5 to 0.9 of self-reporting in cases and controls and drawing a surface plot. Besides, based on point estimation of the sensitivity of reporting opium use, for cases, we considered 0.77 and 0.68 for controls and corrected adjusted ORs are reported.

Statistical analysis

All statistical analyses were conducted using Stata, version 14 (Stata Corp, College Station, TX). Frequencies and percentages were calculated for categorical variables. As we recruited the subjects from ten different centers, heterogeneity between centers was tested (P- heterogeneity) and mixed-effects logistic regression models with random intercept by the center of the study was applied to estimate the association of opium use with HNSCC status (odds ratio with 95% confidence interval). We present adjusted ORs, with the latter adjusted for potential confounders including age, gender, place of residence (center/non-center), cigarette smoking (pack-year), water-pipe smoking (head-year) alcohol drinking (regular drinkers/non-regular drinkers), decayed, missing, and filled teeth (DMFT) index as an indicator of oral health, and socioeconomic status. Socioeconomic status was

determined using principal components analysis, by combining years of education (continuous variable) and ownership of some assets (dichotomous variables; washing machine, freezer, personal computer, sofa, vacuum cleaner, dishwasher, split air conditioner, owned house, owned car). Analyses were conducted for all HNSCC, as well as for four main anatomic sub-sites as introduced above.

Since tobacco and alcohol are two major HNSCC risk factors, we also conducted analyses restricted to those who never tobacco smokers (Supplementary Table 2).

The P-value for multiplicative interaction was obtained employing a Wald test of the interaction coefficient in the logistic regression.

Results

A total of 663 HNSCC cases (254 lip and oral cavity, 54 pharynx, 327 larynx, and 28 other sub-sites within head and neck) and 3065 frequency-matched controls were enrolled in the IROPICAN study. Table 1 shows the distribution of demographic and habit variables in cases and controls. Among cases, approximately 75% were men, 73% were capital city residents, and the median age at recruitment was 58 (25^{th} centile 50 and 75^{th} centile 66 years). The corresponding numbers in controls were 68%, 78%, and 57 (49 – 64) years, respectively. Cases were more likely than controls to smoke, consume alcohol, have lower SES, and have poorer oral health (Table 1). Two percent of cases and 14 percent of controls non-responses were refusals, mostly because of donating blood. No difference in age and gender was observed between participants and non-respondents.

Regular opium use was strongly associated with a higher risk of HNSCC. Table 2 shows the results for the association of regular opium use with all HNSCC combined. The adjusted OR (95% CI) for regular opium use was 3.76 (2.96 to 4.79). There was a strong dose-response association when associations were investigated by the duration of use, cumulative use, and frequency of opium. For example, the OR (95% CI) was 2.06 (1.22 to 3.47) for those who had an above the third tertile of cumulative opium

use (≥24.5 gram-year) among users, as compared to an OR of 2.27 (1.36 to 3.78) for those with the second tertile of cumulative use (3.7-24.5 gram-year).

Both common types of opium used, i.e. crude opium (Teriak) and opium juice (Shireh) were strongly associated with higher HNSCC risk. However, Shireh with an OR (95% CI) of 7.17 (4.44 to 11.58) had a stronger association with HNSCC than Teriak [3.40 (2.64 to 4.37)]. Both routes of opium use, i.e. oral ingestion and smoking were strongly associated with a higher risk of HNSCC. However, oral ingestion, with an OR (95% CI) of 8.33 (4.67 to 14.58) was more strongly associated with HNSCC than smoking [2.66 (2.03 to 3.47)]. The strongest associations were seen in those who used both routes [12.96 (8.14 to 20.62)].

Regular opium use significantly increased the risk of HNSCC of the pharynx, larynx, and other sub-sites within HNSCC, with OR (95% CI) of 2.90 (1.4 to 6.02), 6.55 (4.69 to 9.13), and 5.95 (2.41 to 14.71), respectively (Table 3). A dose-response association was seen for various metrics of opium use with the risk of the larynx and other sub-sites within HNSCC. The association with regular opium use varied between anatomical sub-sites of the larynx; the OR (95%CI) for supraglottis was 18.27 (8.23 to 40.53), glottis 6.20 (3.61 to 10.63), larynx, NOS 4.38 (2.49 to 7.70), and other sub-sites of larynx 7.89 (4.21 to 14.77) (Supplementary Table 1).

By contrast, no statistically significant association was observed for lip and oral cavity squamous cell carcinoma, with an OR (95% CI) of 1.53 (0.97 to 2.41) for regular opium use and of 1.24 (0.44 to 3.43) of cumulative use.

The association of opium use with HNSCC risk persisted among never tobacco smokers (Supplementary 2). The OR (95% CI) for the association between opium use and HNSCC in never smokers was 5.17 (3.26 to 8.21).

Tests for interaction were significant on the multiplicative scale for HNSCC combined that was 8.16 (6.20 to 10.74), lip and oral cavity 1.97 (1.21 to 3.19), pharynx 4.88 (2.09 to 11.41), larynx 28.78 (17.92, 46.21), and other anatomic sub-sites 5.53 (1.70 to 18). Hence, the effect of opium could be varied by cigarette smoking.

According to our sensitivity study, the impact of the sensitivity of self-reporting of opium, 0.77 in cases, and 0.68 in controls indicated that the association of HNSCC combined and regular opium use was still significant, corrected OR was 2.48 (2.05 to 2.98). In addition, the surface plot of corrected OR and sensitivity of self-reporting of opium ranged from 0.50 to 0.90 in both groups showed that the null zone of crude OR did not cross (Figure 1).

Discussion

With over 600 cases and 3000 controls, this study is by far the largest study of opium use and HNSCC conducted to date. Opium use is associated with a remarkably increased risk of HNSCC and some anatomic HNSCC sub-sites, including cancers of the pharynx, larynx, and the other sub-sites group. The risk of cancers of the lip and oral cavity was not increased in regular opium users.

Our findings suggest a causal relationship. We adjusted for important potential confounders, including age, gender, cigarette smoking, water-pipe smoking, alcohol consumption, and SES, nevertheless, the results remained statistically significant. Similarly, when we restricted the analyses to certain subgroups, such as never cigarette and water-pipe smokers, the associations remained significant and strong. There was a clear dose-response association with duration of use, frequency of use, and cumulative use. Compared to more frequent opium users, those who used opium more than 22 times a year were five times more likely to have HNSCC than those used opium eight times a year.

Our findings of an increased risk of HNSCC are in agreement with those of five prior case-control studies [6, 8-11]. The only study that differed was a cross-sectional study of 44 laryngeal cancers. It showed

no association of opium dependency and the pattern of laryngeal anatomic regions [22]. The overall strong consistency of association is again in favor of a causal relationship. The increased risk of HNSCC associated with opium use varied by sub-site. The association was particularly strong for laryngeal cancer, which is consistent with previous literature[6, 8-10]. The potential mechanisms for variations across anatomic sub-sites are unclear.

To rule out the effect of reverse causality on the association of opium use and risk of HNSCC, we reclassified opium users who started opium use three years before diagnosis as non-users. We chose three years, which is longer than most other case-control studies considered, to be sure that even early manifestations of the HNSCC (such as a recurrent wound, coughs, etc.) were not alleviated using opium, particularly for slow-growing tumors [23]. There is other evidence against reverse causality. The large majority of opium users, in both cases and controls, had been using opium for quite a long time; the median duration of regular opium use was approximately twenty years.

Of note, both Teriak and Shireh, the two major types of opium used by our study participants were associated with a higher risk of HNSCC. Likewise, both oral ingestion and smoking of opium were associated with higher HNSCC risk. Both opium ingestion and opium smoking have been associated with higher risk of several cancers, including cancers of the bladder and other sites that do not come into direct contact with opium products[3, 24]. The significance of these findings is not entirely clear, but it may show that it is really the alkaloids in the opium that are the major drivers of carcinogenicity.

Our study has several strengths, including its large sample size; histologic confirmation of all cases; investigating the association by anatomic sub-sites; choosing hospital visitor controls, which were shown to be the appropriate control group to study the effects of opium[16]; using trained investigators, and validated structured questionnaires. The strict control of confounders, by limiting the analyses to never tobacco smokers is another advantage of this study. Using hospital visitor controls turned out

to be the favored option among potential control groups tested in validation study [16]. Especially they showed the most accurate reporting of opium use and also a high response rate.

Our study may have some limitations too. Like other case-control studies, information bias may be a source of biased results. To alleviate this problem, we designed an extensive questionnaire and devised the order of the questions such that neither the interviewers nor the study participants had any preconceived notion that opium was the main study exposure. Likewise, during the training, we did not emphasize the importance of opium in this study. We also tried to minimize interviewer bias using a comprehensive protocol of interviewer training, data collection and monthly reviewing the protocols.

Despite the overall large sample size, some anatomic sub-sites had small sample sizes. We did not have data on HPV infections, an important risk factor for oropharyngeal SCC, which may also be associated with drug use [25-28]. However, only about 7% of Iranian women are positive for cervical HPV [29, 30] and the rates are likely much lower for oropharyngeal HPV. Furthermore, the association of opium and HNSCC were strong among men, who constituted more than two-thirds of our study population and in whom the prevalence of HPV is far lower than women[31]. Therefore, it is unlikely that HPV is a major confounder.

Conclusion

In conclusion, we found evidence of a positive association between opium use and the risk of HNSCC, overall and by most anatomical sub-sites. These findings as add to studies finding cancers of other organs such as bladder, esophagus, and lung related to opium use, suggesting that opium use is an important carcinogen.

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Conflict of Interest

All authors disclosed no financial and personal relationships with other people and organizations that could inappropriately influence (bias) their work.

Data Accessibility

The dataset used in this study is held securely in the coded format at Cancer Research Center (CRC) of Iran. Although data sharing agreements prohibit CRC from making the dataset publicly available, access may be granted to those who meet the conditions for confidential access and on reasonable request via the corresponding author's email (*kzendeh@sina.tums.ac.ir*).

Ethics statement

The study was approved by the Institutional Review Boards of the National Institute for Medical Research Development (IR.NIMAD.REC.1394.027). Written informed consent was obtained.

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Figure Legend

Figure 1- The Surface plot of corrected OR and sensitivity of self-reporting of opium ranged from 0.50 to 0.90 in cases and controls. The plot shows that in both groups the null zone (OR = 1) of crude OR did not cross.

Table 1- Distribution of demographic and habits for head and neck squamous cell carcinoma cases and controls.

	HNSCC Cases * N (%)	Controls N (%)	P-value
Total	663	3065	
Age			0.36
≤29	9 (1.36)	25 (0.82)	
30-39	45 (6.79)	246 (8.03)	
40-49	100 (15.08)	517 (16.87)	
50-59	213 (32.13)	982 (32.04)	
60-69	203 (30.62)	923 (30.11)	
≥70	93 (14.03)	372 (12.14)	
Gender			<0.0001
Male	499 (75.26)	2071 (67.57)	
Female	164 (24.74)	994 (32.43)	
Place of residence			0.007
Capital city	487 (73.45)	2399 (78.27)	
Non-capital city	176 (26.55)	666 (21.73)	
Opium Use [¤]			<0.0001
Non-regular user [‡]	368 (55.51)	2664 (86.92)	
Regular user [§]	295 (44.49)	401 (13.08)	
Cigarette smoking			<0.0001
Non regular-user	292 (44.04)	2220 (72.43)	
Regular user [‖]	371 (55.96)	845 (27.57)	
Pack-years of cigarette smoking	20.82 ± 29.84	5.33 ± 13.14	<0.0001
Water-pipe smoking			
Non regular-user	602 (90.80)	2858 (93.25)	0.02
Regular user[¶]	61 (9.20)	207 (6.75)	
Head-years of water-pipe smoking	48.61 ± 69.12	35.65 ± 65.56	0.08
Alcohol drinking			<0.0001
Non-user	617 (93.06)	2947 (96.15)	
Regular user [#]	46 (6.94)	118 (3.85)	
Socioeconomic status[**]			<0.0001
Low	400 (60.33)	1440 (46.98)	
High	263 (39.67)	1625 (53.02)	
DMFT index [¤□]			<0.0001
Poor [g]	489 (73.76)	1510 (49.27)	
Good	174 (26.24)	1555 (50.73)	

* HNSCC: head and neck squamous cell carcinoma. Cases and controls were frequency matched on age, gender, and place of residence.
¤ Regular opium use: using opium at least once a week for at least a six-month consecutive period during the lifetime.
‡ Non-user included non-regular users

§ After reclassifying opium users who started opium use within three-year prior cancer diagnosis.
‖ Regular cigarette smoking: smoking a cigarette per week for at least a six-month consecutive period during the lifetime.
¶ Regular water-pipe smoking: smoking a head of water-pipe per week for at least a six-month consecutive period during the lifetime.
# Regular alcohol drinking: Drinking any types of alcohol at least once a week for at least a six-month consecutive period during the lifetime.
** We used the median in control subjects as the dividing cut point.
DMFT index: Decayed, Missing, and Filled Teeth index.

Table 2- The associations of opium use with head and neck squamous cell carcinoma.

	HNSCC Cases * N (%)	Controls N (%)	Adjusted OR[¤] (95%CI ‡)
Regular Opium Use §			
Non-user ‖	368 (55.51)	2664 (86.92)	Referent
Regular user ¶	295 (44.49)	401 (13.08)	3.76 (2.96 to 4.79)
P for heterogeneity			<0.0001
Duration of opium use (year)			
1st Tertile (≤11)	51 (17.29)	143 (35.66)	Referent
2nd Tertile (12-23)	101 (34.24)	127 (31.67)	1.68 (1.04 to 2.72)
3rd Tertile (≥24)	143 (48.47)	131 (32.67)	2.52 (1.55 to 4.11)
P trend #			<0.0001
P for heterogeneity			<0.0001
Cumulative use ** (Gram-Year)			
1st Tertile (≤3.6)	38 (12.88)	134 (33.42)	Referent
2nd Tertile (3.7- 24.5)	104 (35.25)	134 (33.42)	2.27 (1.36 to 3.78)
3rd Tertile (≥24.5)	153 (51.86)	133 (33.17)	2.06 (1.22 to 3.47)
P trend			0.022
P for heterogeneity			<0.0001
Frequency-Year ¤¤			
1st Tertile (≤8)	30 (10.17)	138 (34.41)	Referent
2nd Tertile (8.1-22)	52 (17.63)	130 (32.42)	1.70 (0.97 to 2.99)
3rd Tertile (≥23)	213 (72.20)	133 (33.17)	5.09 (3.05 to 8.47)
P trend			<0.0001
P for heterogeneity			<0.0001
Average intensity (Gram/day)			
1st Tertile (≤0.4)	62 (21.02)	150 (37.41)	Referent
2nd Tertile (0.5-2)	110 (37.29)	118 (29.43)	1.33 (0.83 to 2.13)
3rd Tertile (≥2)	123 (41.69)	133 (33.17)	0.88 (0.53 to 1.44)
P trend			0.46
P for heterogeneity			<0.0001
Type of opium used			
Non-user	368 (55.51)	2664 (86.92)	Referent
Crude opium (Teriak)	238 (35.90)	360 (11.75)	3.40 (2.64 to 4.37)
Opium juice (Shireh)	57 (8.60)	41 (1.34)	7.17 (4.44 to 11.58)
P for heterogeneity			<0.0001
Route of opium use			
Non-user	368 (55.51)	2664 (86.92)	Referent
Only smoking	168 (25.34)	337 (11.00)	2.66 (2.03 to 3.47)

Only oral ingestion	35 (5.28)	28 (0.91)	8.33 (4.67 to 14.85)
Both routes	92 (13.88)	36 (1.17)	12.96 (8.14 to 20.62)
P for heterogeneity			<0.0001

* HNSCC: head and neck squamous cell carcinoma. Cases and controls were frequency matched on age, gender, and place of residence.

Random-effect odds ratio. adjusted for age(categorical), gender (categorical), place of residence (categorical), pack-years of cigarette smoking (continuous), head-years of water-pipe smoking (continuous), regular alcohol drinking (categorical), socioeconomic status (categorical), and oral health (DMF index: continuous). Likelihood heterogeneity test by the center.

‡ 95% CI:95% confidence interval.

§ Regular opium use: using opium at least once a week for at least a six-month consecutive period during the lifetime.

‖ Non-user included non-regular users.

¶ After reclassifying opium users who started opium use within three-year prior cancer diagnosis.

P trend: P-values for trend were obtained from adjusted models by assigning values of 1, 2, and 3 to low use (T1), moderate use (T2), and high use (T3), respectively.

** Cumulative use: Total frequency of opium use (per day) multiplied amount (gram) of opium and total duration (year).

Frequency-Year: Total frequency of opium use (per day) multiplied total duration (year).

Table 3- The associations of opium use with head and neck squamous cell carcinoma by anatomical sub-sites.

	Controls N (%)	Lip & Oral Cavity (254 cases)		Pharynx (54 cases)		Larynx (327 cases)		Other sub-sites * (28 cases)	
		Cases N (%)	Adjusted OR ¶ (95%CI)	Cases N (%)	Adjusted OR (95%CI)	Cases N (%)	Adjusted OR (95%CI)	Cases N (%)	Adjusted OR (95%CI)
Regular Opium Use ‡									
Non- user §	2664 (86.92)	221 (87.01)	Referent	37 (68.52)	Referent	96 (29.36)	Referent	14 (50.00)	Referent
Regular user ‖	401 (13.08)	33 (12.99)	1.53 (0.97 to 2.41)	17 (31.48)	2.90 (1.40 to 6.02)	231 (70.64)	6.55 (4.69 to 9.13)	14 (50.00)	5.95 (2.41 to 14.71)
P for heterogeneity			0.28		<0.0001		<0.0001		<0.0001
Duration of opium use (Year)									
1st Tertile (≤11)	143 (35.66)	8 (24.24)	Referent	5 (29.41)	Referent	35 (15.15)	Referent	3 (21.43)	Referent
2nd Tertile (12-23)	127 (31.67)	11 (33.33)	1.01 (0.37 to 2.76)	5 (29.41)	0.93 (0.23 to 3.75)	80 (34.63)	1.91 (1.10 to 3.31)	5 (35.71)	1.89 (0.35 to 10.05)
3rd Tertile (≥24)	131 (32.67)	14 (42.42)	2.09 (0.75 to 5.80)	7 (41.8)	1.9 (0.4 to 8.6)	116 (50.22)	2.71 (1.56 to 4.68)	6 (42.86)	2.96 (0.55 to 15.91)
P trend ¶			0.15		0.40		<0.0001		0.20
P for heterogeneity			0.43		<0.0001		<0.0001		
Cumulative use # (Gram-Year)									
1st Tertile (≤3.6)	134 (33.42)	7 (21.22)	Referent	4 (23.53)	Referent	26 (11.26)	Referent	1 (7.14)	Referent
2nd Tertile (3.7- 24.4)	134 (33.42)	13 (39.39)	1.52 (0.56 to 4.13)	6 (35.29)	1.35 (0.31 to 5.83)	77 (33.33)	2.32 (1.28 to 4.20)	8 (57.14)	9.79 (1.06 to 89.78)
3rd Tertile (≥24.5)	133 (33.16)	13 (39.39)	1.24 (0.44 to 3.43)	7 (41.18)	1.07 (0.22 to 5.08)	128 (55.41)	2.29 (1.26 to 4.16)	5 (35.72)	6.71 (0.65 to 68.99)
P trend			0.73		0.95		0.01		0.13
P for heterogeneity			0.46		<0.0001		<0.0001		<0.0001
Frequency-Year **									
1st Tertile (≤8)	138 (34.41)	11 (33.33)	Referent	3 (17.65)	Referent	14 (6.06)	Referent	2 (14.29)	Referent

2nd Tertile (8.1-22)	130 (32.42)	5 (15.15)	0.41 (0.13 to 1.27)	3 (17.65)	0.99 (0.17 to 5.54)	43 (18.61)	3.38 (1.63 to 6.99)	1 (7.14)	0.31 (0.02 to 4.06)
3rd Tertile (≥23)	133 (33.17)	17 (51.52)	1.24 (0.52 to 2.95)	11 (64.70)	3.24 (0.76 to 13.71)	174 (75.32)	9.05 (4.62 to 17.71)	11 (78.57)	5.53 (1.03 to 29.66)
P trend			0.53		0.07		<0.0001		0.02
P for heterogeneity			0.19		<0.0001		<0.0001		<0.0001

Cont. Table 3- The associations of opium use with head and neck squamous cell carcinoma by anatomical sub-sites.

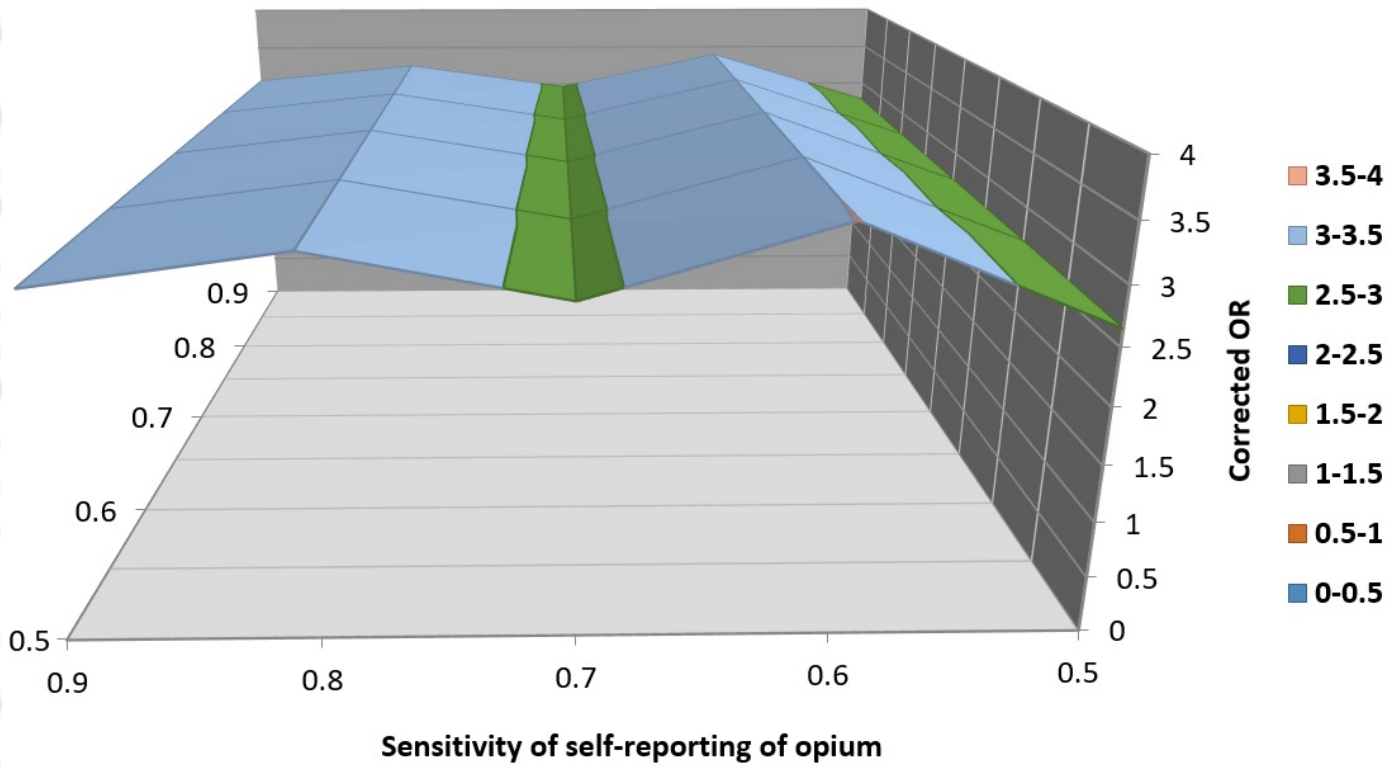
	Controls N (%)	Lip & Oral Cavity (254 cases)		Pharynx (54 cases)		Larynx (327 cases)		Other sub-sites * (28 cases)	
		Cases N (%)	Adjusted OR ¤ (95%CI)	Cases N (%)	Adjusted OR(95%CI)	Cases N (%)	Adjusted OR (95%CI)	Cases N (%)	Adjusted OR (95%CI)
Average intensity (gram/day)									
1st Tertile (≤0.4)	150 (37.40)	7 (21.21)	Referent	5 (29.41)	Referent	44 (19.05)	Referent	6 (42.86)	Referent
2nd Tertile (0.5-2)	118 (29.43)	15 (45.45)	2.28 (0.869 to 6.03)	8 (47.06)	1.63 (0.48 to 6.51)	83 (35.93)	1.27 (0.74 to 2.16)	4 (28.57)	0.80 (0.19 to 3.34)
3rd Tertile (≥2)	133 (33.17)	11 (33.34)	1.12 (0.39 to 3.19)	4 (23.53)	0.41 (0.07 to 2.26)	104 (45.02)	0.92 (0.53 to 1.60)	4 (28.57)	0.82 (0.19 to 3.42)
P trend			0.96		0.26		0.62		0.77
P for heterogeneity			0.52		<0.0001		<0.0001		<0.0001
Type of opium used									
Non-user	2664 (86.92)	221 (87.01)	Referent	37 (68.52)	Referent	96 (29.36)	Referent	14 (50.00)	Referent
Crude opium (Teriak)	360 (11.75)	28 (11.02)	1.41 (0.87 to 2.27)	15 (27.78)	2.81 (1.32 to 5.97)	182 (55.66)	5.77 (4.09 to 8.15)	13 (46.43)	6.04 (2.43 to 15.05)
Opium juice (Shireh)	41 (1.33)	5 (1.97)	2.90 (1.05 to 7.97)	2 (3.70)	3.77 (0.80 to 17.68)	49 (14.98)	12.69 (7.25 to 22.22)	1 (3.57)	4.83 (0.55 to 41.97)
P for heterogeneity			0.37		<0.0001		<0.0001		0.002
Route of opium use							<0.0001		<0.0001
Non-user	2664 (86.92)	221 (87.01)	Referent	37 (68.52)	Referent	96 (29.36)	Referent	14 (50.00)	Referent
Only smoking	337 (11.00)	20 (7.87)	1.09 (0.64 to 1.86)	15 (27.78)	3.04 (1.43 to 6.47)	125 (38.23)	4.28 (2.98 to 6.14)	8 (28.58)	3.97 (1.44 to 10.99)
Only oral ingestion	28 (0.91)	6 (2.36)	4.25 (1.45 to 11.69)	1 (1.85)	2.67 (0.33 to 21.57)	25 (7.65)	17.17 (8.44 to 34.91)	3 (10.71)	17.92 (4.32 to 74.26)
Both routes	36 (1.17)	7 (2.76)	5.10 (2.41 to 12.89)	1 (1.85)	1.74 (0.21 to 14.26)	81 (24.77)	25.11 (14.55 to 43.33)	3 (10.71)	11.96 (2.83 to 50.52)
P for heterogeneity			0.17		<0.0001		<0.0001		<0.0001

* Other sub-sites included pyriform sinus, nasal cavity, and middle ear, accessory sinuses, and head & neck, NOS.

¤ Random-effect odds ratio. adjusted for age(categorical), gender (categorical), place of residence (categorical), pack-years of cigarette smoking (continuous), head-years of water-pipe smoking (continuous), regular alcohol drinking (categorical), socioeconomic status (categorical), and oral health (DMF index: continuous). Likelihood heterogeneity test by the center.

‡ Regular opium use: using opium at least once a week for at least a six-month consecutive period during the lifetime.
§ Non-user included non-regular users.
‖ After reclassifying opium users who started opium use within three- year prior cancer diagnosis.
¶ P trend: P-values for trend were obtained from adjusted models by assigning values of 1, 2, and 3 to low use (T1), moderate use (T2), and high use (T3), respectively.
# Cumulative use: Total frequency of opium use (per day) multiplied amount (gram) of opium, then multiplied total duration (year).
** Frequency-Year: Total frequency of opium use (per day) multiplied total duration (year)

Opium use has been associated with the risks of several cancers, but there is little data on whether opium contributes to head and neck cancer risk. Here, the authors conducted a multicenter case-control study, the Iran Opium and Cancer study (IROPICAN). They recruited 633 cases of head and neck squamous cell carcinoma and 3065 controls. The study drew from 10 provinces in Iran where opium use is most prevalent. They found that regular opium users have an elevated overall risk of HNSCC, and laryngeal cancer in particular.



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