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Oral health and the risk of head and neck squamous cell carcinoma: a multicenter case-control study in Iran

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The current study aimed to assess the independent effect of a high Decayed, Missing, and Filled Teeth (DMFT) score on the risk of head and neck squamous cell carcinoma (HNSCC) overall and its subsites. Also, we tested for the interaction effect of smoking tobacco and opium with the DMFT score on the risk of developing HNSCC. We included 899 pathologically confirmed cases of HNSCC and 3477 healthy visitor controls. We used multivariable unconditional logistic regression analyses to estimate odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for study centers, age, sex, socioeconomic status, and alcohol, cigarettes, water pipes, and opium use. We found an OR of 2.0 (95% CI: 1.6, 2.5) between DMFT scores higher than 17 and the risk of HNSCC. This was higher for laryngeal (OR: 3.6, 95% CI: 2.5, 5.2) than lip oral cavity (OR: 1.5, 95% CI: 1.2, 2.0) cancers. We found a positive association between Decayed and Missing teeth, however, it was reversed for the number of Filled teeth. The association for those who had higher DMFT score was significantly higher (OR: 2.3, 95%CI: 1.7, 3.0) among smokers than non-smokers (OR: 1.7, 95% CI: (1.2, 2.3). A higher DMFT score was associated with an increased risk of HNSCC, with an interaction between DMFT score and smoking.

Keywords HNSCC, Oral health, Opium, Tobacco

Abbreviations

CIs	Confidence intervals
DMT	Decayed and missing teeth
DMFT	Decayed, missing, and filled teeth
HNSCC	Head and neck squamous cell carcinoma
HNC	Head and cancer
IROPICAN	The Iranian study of opium and cancer
ORs	Odds ratios
SES	Socioeconomic status

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Background

Head and neck cancer (HNC) with an of 10.1 per 100,000 is the seventh most common cancer in 2020. Melanesia and South-central Asia have the highest HNSCC incidence all over the world with an age-standardized incidence rate of 21.8 and 16.2 per 100,000 respectively. Substantial increasing incidence and mortality trends of HNC have been demonstrated in many populations. However, the temporal change varied by HNC subsite and country[1].

Smoking and alcohol drinking are well-established risk factors for HNC; the synergic effect between them has been indicated as a trigger for the risk of HNC[2,3]. However, a large part of HNC cases is not attributable to alcohol and tobacco, especially for cases originating from oral cavity cancer, in women and young patients[3] A large proportion of oral cavity cancers are attributed to Chewing betel quid in the Pacific islands and South and Southeast Asia[4,5]. Opium is another important risk factor for laryngeal and pharyngeal cancers in regions like Iran with a high prevalence of its use[6,7].

Numerous epidemiological studies have shown an increased risk of HNC for poor oral hygiene[8,9]. Oral health indicators such as dental caries, tooth loss, and periodontal disease, are identified as possible risk factors for HNC[8,10]. The results of a recently published meta-analysis suggest that tooth loss may be an independent and substantial risk factor for HNC, even after adjusting for smoking and alcohol use. However, more investigations for finding a causative relation and assessment of the interactions between risk factors to find new approaches for prevention and treatment were suggested[11].

Our study aims to explore the association between oral health and the risk of Head and Neck Squamous Cell Carcinoma (HNSCC) and its subsites using data from the Iran Opium and Cancer study (IROPICAN), a large case-control study with more than 5000 subjects[12], after adjusting for the confounding effect of smoking, and to evaluate the interaction between smoking and poor oral health.

Methods

Cases and control selection

A total number of 899 histopathological confirmed HNSCC cases and 3477 controls were recruited from ten provinces of Iran from May 2017 to July 2020. We recruited incident and primary cases of HNSCC cases from referral centers for cancer treatment. We categorized cases by tumor site using the International Classification of Diseases for Oncology, third edition (ICDO-3). We included cancers of the lip and oral cavity (C00-C08 and C14), pharynx (C09-C11 and C13), larynx (C32), and other subsites within the head and neck (C12, C30-C31, and C76). The control group consisted of hospital visitors selected among next-of-kin of non-cancer patients in referral wards of hospitals. The IROPICAN study is a multicenter case-control study that investigates the association between opium use and the risk of lung, colorectal, bladder, and head and neck cancers and controls of all studied cancer types combined were frequency matched by sex, age (five year intervals), and residential places (by province and capital city/non-capital city). The matching was not perfect, as the controls were slightly younger than the cases, also matched with the cases of all studied cancer types combined. More details about the case and control selection procedures have been reported[12].

Oral health variables

Oral health examination was done by trained interviewers who had received comprehensive training on the oral health examination protocol under the supervision of an oral health care specialist. The training program included a combination of theoretical and practical sessions, and was led by a senior dentist with expertise in oral health. The interviewers used a standardized data collection form to record the findings, which was reviewed and validated by the study team before use.They were trained to assess the teeth visually, using a dental mirror and a probe. The oral examinations for cases was done before receiving treatment and on hospital beds. The controls were directed to the interview room and their oral examination was done on a comfortable chair. In each study center, there was one oral examiner who was well instructed by a dentist. There was a detailed protocol for oral examinations and all examiners were trained by the same person through workshops. A random sample of the examinations was checked by the senior dentist to ensure consistency and accuracy. The oral health examination protocol was designed to ensure consistency and accuracy in data collection, and was based on standard oral health assessment criteria (Supplemetary material1).

The number of decayed teeth was defined using cut-offs based on density graphs of the control population, <7 or ≥ 7, that of missing teeth as <5, 5–14 and <14, and that of filled teeth as <2, 2–5, and >5. Wearing dentures was defined dichotomously. We calculated the Decayed, Missing, and Filled teeth (DMFT) score by summing the numbers of decayed, missing, and filled teeth[13]and used the median score of the control group as the cut point. Besides, we calculated the Decayed and Missing Teeth (DMT) score as the sum of the decayed and missing teeth and categorized it based on the median score in the control group.The cutoff value for DMFT score (≥ 17) was selected based on the median value in the control population, using density plots to identify natural breakpoints. Using the median as a cutpoint is a simple method for dichotomizing continuous variables[13]. On the other hand, considering the context of our research, for example, a 2024 national pathfinder survey of Tanzanian adults (ages 30–50+) reported a mean DMFT of **4.63 (SD 5.4)**, with caries prevalence at **76.6%**. While below 17, this value in a very resource-limited context underscores how substantially higher scores (e.g.,$\geq$ 17) reflect severe, untreated disease[14].

Covariates

Covariates included age (5-year age categories above age 30), sex, residential place (capital city/Non-capital city), and socioeconomic status (SES; low/ medium/ high). The principal component 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) was used to derive SES[7]. We used tertiles in the control group as cut points.

Other covariates include alcohol use (ever/never), water pipe smoking (ever/never), average cumulative lifetime consumption of cigarettes (0–15, 15–31, 31 + pack-years), cumulative lifetime frequency of opium use (< 4900, 4900 – 1950, 1950 + times lifetime), and fruit and vegetable intakes, which were included as continuous variables expressed as g/day.

We collected detailed substance (opium, alcohol, cigarettes, and other tobacco) use histories from both cases and controls. We asked them about their ages when they started and stopped using opium, how much, and how often they used it. We used these durations as weights to calculate weighted averages.

Dietary intakes were assessed with validated qualitatively Persian Cohort food frequency questionaire administered by trained interviewers[15]. To calculate the consumption of fruits and vegetables, the reported frequency of consumption (daily, weekly, monthly, or yearly) was converted to frequency per day and was multiplied by the standard portion size (grams) using household measures.

Statistical analyses

We used univariate unconditional logistic regression analyses to estimate the crude odds ratios and multivariable unconditional logistic regression to estimate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of HNSCC. We assumed the first level of scores as the reference group which was the lowest count of decayed, missing, filled, DMFT, and DMT scores in all analyses.

To adjust for the potential confounding effect of other risk factors, we considered water pipe smoking, cigarette smoking, opium use, and SES in the regression models. We did not include alcohol use, and fruit and vegetable consumption in our final model, because it did not improve its fitness ($p > 0.1$). To adjust for the clustering effect of different centers in the study, we adjusted the results by province. To assess the multiplicative interaction between smoking tobacco or opium and DMFT score we used the interaction term in the models. Moreover, we repeated all the analyses by smoking status of participants as well. To investigate the additive interaction of tobacco use only and opium use only with high DMFT score on HNSCC risk, we analyzed the combined effect of each substance separately with high DMFT score on the risk of developing HNSCC.

All statistical analyses were conducted using Stata, version 14 (Stata Corp, College Station, Texas).

Results

We included 899 HNSCC cases and 3477 controls. The distribution of demographic and behavioral variables of cases and controls are presented in Table 1. Most of the cases were male (75%), from the non-capital city of the provinces (70%); the median age at recruitment was 59 (interquartile range 51–66). As well controls were mostly male (69%), from the non-capital city of the provinces (62%), with a median age of 58 (interquartile range 50–65).

Results for all HNSCC cases

Table 2 shows the OR of HNSCC for oral health indicators. The OR for 7 or more decayed teeth compared to less than 7 decayed teeth was 1.5 (95% CI:1.2,2.0). The OR for those with 14 or more missing teeth compared to less than 5 missing teeth was 1.7 (95% CI:1.3,2.3) and the association was significantly higher among smokers 2.0 (1.4,2.7) than non-smokers 1.5 (1.0,2.1).

The number of filled teeth had a reverse association with HNSCC risk, as having filled teeth between 2 and 5 (OR: 0.4, 95% CI: 0.3, 0.6) and more than 5 lower the risk of HNSCC (OR: 0.5, 95% CI: 0.3, 0.7) compared to those had less than 2 filled teeth (Table 2).

Those with a DMFT score of more than 17 had a two-fold increased risk of HNSCC (OR: 2.0, 95% CI: 1.6, 2.5) compared to those with a DMFT score equal to or less than 17. Similarly, subjects with a DMT score of more than 14 had an OR of 1.9 (95% CI: 1.5–2.3) compared to the low-risk group (< = 14). There was a multiplicative interaction between smoking (opium/cigarette) and poor oral health with HNNSCC ($p < 0.05$)Although an association between denture use and HNSCC was present in the crude analyses (OR: 1.4, 95% CI: 1.2, 1.7; result not shown), it was no longer present after adjusting for confounders (OR: 1.0, 95% CI: 0.8, 1.2; Table 2).

We found that among only tobacco users, those with high DMFT score had a significantly increased risk of HNSCC (OR: 3.00, 95% CI: 2.47–3.66) compared to those with low DMFT score and the relative excess risk due to interaction was 1.08 (0.80,1.36). Among only opium users, those with high DMFT score had a significantly increased risk of HNSCC (OR: 8.68, 95% CI: 5.12–14.73) compared to those with low DMFT score (RERI: 5.81, 95% CI: 1.25–10.38), indicating a synergistic effect between opium use and high DMFT score on HNSCC risk (Table 4).

Among users of both opium and tobacco, those with high DMFT score had a significantly increased risk of HNSCC (OR: 15.60, 95% CI: 11.35–21.45) compared to those with low DMFT score. The RERI was also significant for the combination of opium and tobacco use with a high DMFT score (RERI: 11.21, 95% CI: 6.84–15.57), indicating a strong synergistic effect between these factors on HNSCC risk (Table 4).

Results by HNSCC subsites

Higher DMFT score was associated with an increased risk of cancer of the larynx (OR: 3.6, 95% CI: 2.5, 5.2) and of the lip and oral cavity (OR: 1.5, 95% CI: 1.2, 2.0), while the association was not significant for pharyngeal cancer cases (OR: 1.7, 95% CI: 1.0, 2.8; Table 3).

Considering the smoking status, the strength of the association among non-smokers was reduced for laryngeal cancer (OR: 2.2, 95% CI: 0.9, 5.5) but not for lip and oral cavity cancer (OR: 1.7, 95%CI: 1.2, 2.6) or for pharyngeal cancer (OR 1.6; 95%CI 0.8–3.3; Tables 3 and 4).

Variable	Controls N (%)	Cases N (%)
Total	3477	899
Age (years)		
30–39	257 (7.4)	61 (6.8)
40–49	559 (16.1)	142 (15.8)
50–59	1070 (30.8)	272 (30.3)
60–69	1092 (31.4)	290 (32.3)
≥ 70	499 (14.3)	134 (14.9)
Gender		
Female	1077 (31.0)	223 (24.8)
Male	2400 (69.0)	676 (75.2)
Place of residence		
Non-capital city	2167 (62.3)	631 (70.2)
Capital city	1310 (37.7)	268 (29.8)
Province		
Tehran	816 (23.5)	162 (18.0)
Fars	1027 (29.5)	379 (42.2)
Kerman	525 (15.1)	158 (17.6)
Golestan	374 (10.7)	40 (4.4)
Mazandaran	136 (3.9)	17 (1.9)
Kermanshah	251 (7.2)	37 (4.1)
Khorasan-Razavi	170 (4.9)	37 (4.1)
Hormozgan	78 (2.2)	33 (3.7)
Systan-Balouchestan	100 (2.9)	36 (4)
SES [a]		
Low	974 (28.0)	355 (39.5)
Medium	1174 (33.8)	297 (33.0)
High	1329 (38.2)	247 (27.5)
Smoking status		
Never smoker	1951(56.1)	259 (28.8)
Ever smoker of Opium /Tobacco	1526 (43.9)	640 (71.2)
Total fruit consumption (g/day; mean (SD))	334 (254)	307 (308)
Total vegetable consumption (g/day; mean (SD))	486 (289)	445 (352)

Table 1. Distribution of demographic and behavioral variables for head and neck squamous cell carcinoma cases and controls (Iran, May 2017 - July 2020). [a]We used tertiles in control subjects as the cut-point [b] Never users are individuals who have never used any tobacco products, including cigarettes, waterpipes, or opium, throughout their lifetime

Discussion

Higher DMFT score was associated with an increased risk of HNSCC after adjusting for tobacco and opium use and other possible confounders. Analyzing the values for DMFT score showed that decayed and missing teeth are risk factors for HNSCC while filled teeth showed an inverse association with HNSCC risk. There were not a significant association between denture use and the risk of HNSCC after adjusting the results for smoking. The association between DMFT score and lip and oral cavity remained significant even when we restricted the analyses to never-smokers. There was an apparent multiplicative interaction between ever smoking (opium or tobacco) and poor oral health indices including DMFT score and number of feeling and missing teeth.

We observed a significant association between the use of opium, either alone or in combination with tobacco, and an increased risk of head and neck squamous cell carcinoma (HNSCC), particularly among individuals with poor oral health, as indicated by high DMFT score. Notably, tobacco use alone also showed a similar, albeit weaker, interaction with high DMFT score concerning HNSCC risk. Poor oral health was a risk factor for oral cancer even among non-smokers, however, it was not associated with laryngeal cancer after restricting the analyses to non-smokers.

We detected an increased risk of laryngeal cancer for high DMFT score among all study population but the association disappeared when we restricted the analyses to never smokers. It seems that the association appeared to be explained by tobacco smoking and opium use; indeed 93% of our patients with laryngeal cancer cases were smokers while only 47% of oral cancer cases were smokers. which is in line with previous studies results, that almost all patients with laryngeal cancer (98%) had a history of smoking[16]. Our research findings revealed a significant association between tooth decay (dental caries) and an elevated risk of head and neck squamous cell carcinoma (HNSCC). If left untreated, dental caries ultimately lead to tooth loss, accounting for approximately

	All study population				Ever Smokers of Opium /Tobacco			Never smokers		
	Controls	Cases	Adjusted OR[a] (95%CI)	Controls	Cases	Adjusted OR[a] (95%CI)	Controls	Cases	Adjusted OR[a] (95%CI)	P for heterogeneity
Number of decayed teeth										
< 7	3149 (90.6)	764 (85.0)	Ref	1339 (87.7)	539 (84.2)	Ref	1810 (93.0)	225 (87.0)	Ref	
≥ 7	328 (9.4)	135 (15.0)	1.5 (1.2,2.0)	187 (12.2)	101 (15.8)	1.3 (1.0,1.8)	141 (7.2)	34 (13.1)	2.1 (1.4,3.2)	0.1
Number of missing teeth										
< 5	996 (28.6)	157 (17.5)	Ref	355 (23.3)	76 (11.9)	Ref	641 (32.8)	81 (31.3)	Ref	
5–14	954 (27.4)	142 (15.8)	1.0 (0.8,1.3)	379 (24.8)	83 (13.0)	1.2 (0.8,1.7)	575 (29.5)	59 (31.3)	0.9 (0.6,1.3)	0.3
≥ 14	1527 (43.9)	600 (66.7)	1.7 (1.3,2.3)	792 (51.9)	481 (75.2)	2.0 (1.4,2.7)	735 (37.7)	119 (46.0)	1.5 (1.0,2.1)	< 0.05
Number of filling teeth [b]										
< 2	2383 (68.5)	783 (87.1)	Ref	1146 (75.1)	589 (92.0)	Ref	1237 (63.4)	194 (74.9)	Ref	
2–5	635 (18.3)	66 (7.3)	0.4 (0.3,0.6)	219 (14.3)	28 (4.4)	0.4 (0.3,0.6)	416 (21.3)	38 (14.7)	0.5 (0.3,0.8)	< 0.05
≥ 5	459 (13.2)	50 (5.6)	0.5 (0.3,0.7)	161 (10.5)	23 (3.6)	0.5 (0.3,0.8)	298 (15.3)	27 (10.4)	0.5 (0.3,0.8)	< 0.05
DMFT score[c]										
≤ 17	1781 (51.2)	239 (26.6)	Ref	643 (42.1)	114 (17.8)	Ref	1138 (58.0)	125 (48.3)	Ref	
> 17	1696 (48.8)	660 (73.4)	2.0 (1.6,2.5)	883 (57.9)	526 (82.2)	2.3 (1.7,3.0)	813 (41.7)	134 (51.7)	1.7 (1.2,2.3)	< 0.05
DMT score[d]										
≤14	1746 (50.2)	234 (26.03)	Ref	620 (40.6)	109 (17.0)	Ref	1126 (57.7)	125 (48.3)	Ref	
>14	1731 (49.8)	665 (73.97)	1.9 (1.5–2.3)	906 (59.4)	53 (83.0)	2.0 (1.5,2.7)	825 (42.3)	134 (51.7)	1.7 (1.2,2.3)	< 0.05
Denture Use										
No	2005 (57.7)	456 (50.7)	Ref	829 (54.3)	308 (48.1)	Ref	1176 (60.3)	148 (57.1)	Ref	
Yes	1138 (32.7)	372 (41.4)	1.0 (0.8,1.2)	569 (37.3)	291 (45.5)	1.0 (0.8,1.2)	569 (29.2)	81 (31.3)	1.0 (0.8,1.5)	0.1
Unknown	334 (9.6)	71 (7.9)	1.0 (0.7,1.4)	128 (8.4)	41 (6.4)	-	206 (10.6)	30 (11.6)	-	-

Table 2. The association of oral health with head and neck squamous cell carcinoma among all study population, ever smokers of tobacco /opium and never smokers in Iran from May 2017 to July 2020. [a] Odds ratio adjusted for age (categorical), gender (male/female), province, pack-years of cigarette use (categorical), regular water-pipe use (yes/no), cumulative count of opium use (categorical), socioeconomic status (low/medium/high). [b] We used 75th and 90th percentile of the control group as cut points for filling teeth using density graphs. [c] DMFT score: sum of the number of decayed missing and filled teeth. we used median in control group as the cut point. [d] DMT score: sum of the number of decayed and missing teeth.

	Lip&oral cavity			Pharynx [e]			Larynx		
Smoking Status	Case (exposed/unexposed)[a]	Control (exposed/unexposed)[a]	Adjusted OR (95% CI)	Case (exposed/unexposed)[a]	Control (exposed/unexposed)[a]	Adjusted OR (95% CI)d	Case (exposed/unexposed)[a]	Control (exposed/unexposed)[a]	Adjusted OR (95% CI)
All study popualtion	136/183	1781/1969	1.5 (1.2,2.0)[c]	40/46	1781/1969	1.7 (1.0,2.8)[c]	48/388	1781/1969	[c] (2.5,5.2) 3.6
Ever smokers of Opium / Tobacco	57/94	643/883	[c] (0.9,2.1) 1.4	14/31	643/883	[c](0.8,3.7) 1.8	38/371	643/883	[c] (2.5,5.7) 3.8
Never smokers[b]	79/89	1138/813	1.7 (1.2,2.6)[d]	26/15	1138/813	1.6 (0.8,3.3)[d]	10/17	1138/813	[d](0.9,5.5) 2.2

Table 3. The association of oral health by head and neck squamous cell carcinoma subsite among all study population, ever smokers of tobacco /opium and never smokers in Iran from May 2017 to July 2020. [a] Exposed group are those with a high DMFTscore and unexposed are those with low DMFTscroe. [b] never smoker were defined as thise who does not smoke tbacco or use opium during theril lifetime. [c] Odds ratio adjusted for age (categorical), gender (male/female), province, pack-years of cigarette use (categorical), regular water-pipe use (yes/no), cumulative count of opium use (categorical), socioeconomic status (low/medium/high). [d] Odds ratio adjusted for age (categorical), gender (male/female), province and socioeconomic status (low/medium/high). [e] p-value for heterogenity was less than 0.05 for laryngeal cancer.

40% of extracted teeth[17,18]. Moreover, The presence of dental caries indicates poor oral hygiene and highlights the substantial bacterial infection within the oral cavity[19].

The link between oral hygiene and oral cancer has been studied for a long time, but the findings are not clear[20,21]Tobacco and alcohol use are the main causes of oral cancer, and they also affect dental health. This

		Never use of anything		Users	
	Oral Health	Cases/Controls	OR (95% CI) [a]	Cases/Controls	OR (95% CI) [a]
Only Tobacco	Low DMFT	133/1210	Ref.	63/425	1.34 (0.96,1.87)
	High DMFT	145/887	1.59 (1.19,2.11)	146/497	3.00 (2.47,3.66)[b]
Only Opium	Low DMFT	133/1210	Ref.	6/14	2.12 (0.85,5.31)
	High DMFT	145/887	1.75 (1.29,2.37)	33/64	8.68 (5.12,14.73)[c]
Opium and Tobacco	Low DMFT	133/1210	Ref.	159/1239	3.92 (2.45,6.27)
	High DMFT	145/887	1.47 (1.09,1.99)	466/1057	15.60 (11.35,21.45)[d]

Table 4. Interaction between tobacco, opium, and oral health on head and neck squamous cell carcinoma in Iran from May 2017 to July 2020. [a]Adjusted for age, gender, province, and socioeconomic status [b]Relative excess risk due to interaction (RERRI) was 1.08 (0.80,1.36). [c] RERRI was 5.81 (1.25,10.38). [d]RERRI was 11.21 (6.84,15.57). RERI is equal to OR (AB) - OR (Only A)-OR (Only B) + 1 in the absence of interaction, RERI is equal to zero.

makes it hard to tell if DMFT score is related to oral cancer or not[22,23], but the results of our study showed an independent association between high DMFT score and the risk of oral cancer.

We found a 1.7-fold increased risk of developing HNSCC for 14 or more missing teeth compared to less than 5. This is in line with the results of the other studies. Tooth loss is associated with an increase in the risk of developing HNSCC[24,25] and in particular oral cancer[8,26]. The magnitude of the excess risk of HNSCC in patients with tooth loss reported in the literature is similar to the one we detected. According to a recently published meta-analysis, those with tooth loss had higher risk of developing HNSCC (OR: 2.13, 95% CI: 1.63,2.78)[11]. Furthermore, a strong correlation exists between oral cancer and the number of missing teeth[22,27].

Tooth loss which can be a precursor for HNSCC through a direct and indirect mechanism. In direct effect, bacterial infection may lead to increased levels of nitrosamines[28] and acetaldehyde levels[29–31]; these agents are involved in developing chronic diseases such as cancers[29,30]. In addition, toxins and reactive oxygen species produced by oral bacteria may promote carcinogenesis[32,33]. In an indirect mechanism, chronic infection can cause systemic inflammation[34–36]. There is strong evidence to support the hypothesis of an etiologic role of microbial infection in the oral cavity on oral cancer[37].

Filled teeth had a protective effect on the risk of HNSCC in our study. In almost all studies, filled teeth have been included in the DMFT score and have not been analyzed independently.

Qin et al.[38]. In our study, there was a significant negative correlation (r=-0.44, $p < 0.0001$) between DMT score and filled teeth. Which shows those who have more filled teeth have less decayed and missed teeth. This result s.

Therefore, filled teeth as included in DMFT score, although well represent the dental status in populations but may not be suitable for scoring the oral hygiene. Thus, we suggest excluding filled teeth from the DMFT score when investigating the oral hygiene status and exploring its association with HNSCC and other pathologic conditions. Regarding this concept, we calculated the DMT score and analyzed its association with HNSCC. The result was somehow similar to that of the DMFT score since the number of filled teeth was generally low in this population.

Denture use was not associated with the risk of HNSCC, consistent with the previous publications[39,40]. Specifically, the literature suggests that defective dentures, rather than dentures per se, are associated with an increased risk of oral squamous cell carcinoma (OSCC)[41], however, we did not assess the condition of dentures worn by participants, which may have introduced bias into our analysis. Denture use is not a direct risk factor for HNSCC, but it may cause irritation or infection of the oral mucosa, which could increase the risk of developing cancer[42]. On the other hand, lesions caused by dentures have been associated with tongue cancer[23,43], as well as gastric cancer[44].

We detected a multiplicative interaction between tobacco smoking or opium use and a high DMFT score.

smoking can accelerate the carcinogenic effect of poor oral health through different mechanisms. Smoking exacerbates inflammation in the oral cavity, potentially promoting cancer development. In addition, smoking-related toxins can damage oral tissues and DNA, increasing susceptibility to cancer. Smoking weakens the immune response, allowing cancer cells to proliferate and alters the oral microbiome, which may influence cancer risk[45]. To our knowledge, this is the first study that assessed and found a strong interaction between smoking tobacco, opium use, and poor oral health.

This interaction effect could be also responsible for the strong effect of high DMFT score in laryngeal cancer and preventive efforts to encourage smoking cessation are likely to represent an important strategy to reduce the incidence of HNSCC and specifically laryngeal cancer.

The current study had several strengths. Oral health examinations were performed by trained interviewers and data were collected through a comprehensive protocol and we collected detailed information about smoking tobacco and opium as the main risk factors of HNSCC, this is the first study showing the effect of oral health on HNSCC risk in relation to smoking tobacco and opium use. All included cases were pathologically confirmed and information about specific types of HNSCC was available while in previous studies information about the specific types of HNSCC was not available[11]. Due to the large sample size of the current study, we could assess the oral health and HNSCC association by subsites and smoking status (tobacco and opium). Even though previous studies included smoking and adjusted for them, the residual confounding of smoking cannot be ruled

out[11]. To control for the possible residual confounding effect of the smoking opium or tobacco, as the major confoundes, we repeated the analyses among never-smokers.

The present study has some limitations. The confidence intervals are wide, in particular for the missing teeth the study's results should be interpreted with caution, and further research with more precise estimates of the association between some indicators such as missing teeth and the risk of head and neck squamous cell carcinoma.

Oral examinations were done after the occurrence of cancer; also we did not collect data on time since decayed, missing, or filled teeth, however, we included the incidence cases of HNSCC and it is unlikely that they are the consequence of cancer. In the current study, we did not collect information about periodontitis as one of the oral health indicators wich could result in residual confounding, however, a substantial part of oral health conditions can be explained by tooth loss. Moreover, we did not collect data on plaque index and oral hygiene habits (brushing/flossing), and studies showed that those who have high plaque and rarely brush their teeth have significantly higher DMFT index[46,47]. Possible selection bias is the other limitation, as cases and controls may not be from the same underlying population, to overcome this issue we matched cases and controls by their residential places, moreover we adjusted the reults by residential places. Not having a complete response rate among cases (98%) and controls (88%) could be the other source of selection bias however, the distribution of demographic variables such as age, gender, marital status, and education was approximately the same between respondents and non-respondents. In our validation study, we found a similar underreporting proportion for opium use as an illegal substance between cases and controls[48], and the same is possible for alcohol use. On the other hand, the prevalence of alcohol use among controls in the current study was similar to the Iranian Mental Health Survey (IranMHS) 2011 (4.1% versus 5.7%)[49]. Overall, cases are more prone to report perceived hazardous exposures, and information bias is possible.

Regarding the interaction between smoking and DMFT score, more research is needed to explore the mechanistic pathway of these two factors. To find out if avoiding oral disease can lower the chances of getting head and neck cancer, more studies are needed. Future research should measure oral health directly and objectively, and also look at the types of microbes in the mouth, the signs of inflammation in the body, and how the immune system reacts to long-term inflammation."

In conclusion, our findings indicate that tooth loss and decayed teeth as oral health indicators can be independent risk factors for HNSCC. However, the multiplicative interaction between tobacco and opium use with the DMFT score emphasizes the importance of tobacco smoking and opium use, which substantially aggravates this association. Results on DMFT score emphasize the importance of dental clinic visits on the HNSCC. These results could help clinicians understand better what causes HNSCC and how to prevent and treat it. Therefore, this report could be useful for clinical practice that focuses on oral health, identifying patients who have a high risk of HNSCC, and making policies that encourage oral health care."

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Author contributions

K.Z, and S.M were involved in the conceptualization of the study. H.R, E.M, M.H, M.S, and K.Z did the data curation. Formal analysis was done by H.R, K.Z, E.M. K.Z was involved in Funding acquisition. The investigation was done by H.R, M.G, E.M, MS.S, and M.H. AA.H, and K.Z were involved in Methodology. Writing the original draft was done by S.M, H.R, K.Z, E.M, and PB. review & editing of the manuscript was done by all of the authors.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

The study was approved by the Ethics Committee of the National Institute for Medical Research Development (NIMAD) of Iran (Code: IR.NIMAD.REC.1394.027). All participants signed written informed consent to participate in the study. All procedures were conducted following the appropriate guidelines and regulations.

Consent for publication

Not applicable.

Additional information

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