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Original Article

Evaluation of Risk Factors in Patients with Head and Neck Cancer: A Case Control Study

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Abstract

Background: Head and neck squamous cell carcinoma (HNSCC) is one of the most common types of cancer worldwide. Since there are many factors that influence the development of cancer, identifying risk factors plays an important role in cancer prevention. The aim of this study was therefore to identify the risk factors for HNSCC in Mashhad, Iran.

Methods: In this case-control study, 76 patients with HNSCC were included as the case and 91 healthy people as the control group. A checklist of risk factors was completed for each participant and the two groups were compared for the presence of risk factors. Chi-square, *t* test, and Mann-Whitney tests were used to compare the data. Odds ratios (ORs) for several factors have also been determined.

Findings: The educational level and body mass index (BMI) of the patients in the case group were significantly lower than in the control group ($P<0.001$). Moreover, there were significant differences between the two groups in terms of risk factors such as tobacco smoking, the number of cigarettes smoked per day, and its duration ($P=0.001$, $P<0.001$, $P=0.05$), as well as the duration of hookah smoking, opium consumed per day and use of alcohol ($P=0.023$, $P<0.001$, $P=0.015$).

Conclusion: There was a direct relationship between HNSCC and risk factors such as cigarette smoking, number of cigarettes smoked per day, duration of cigarette consumption and hookah, opium consumed per day, and alcohol use. However, extensive studies with larger sample sizes are needed to better assess the impact of these factors and generalize the results.

Keywords: Carcinoma, Squamous cell, Head and neck neoplasms, Risk factors, Smoking, Alcohols, Body mass index

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Introduction

Despite advances in cancer treatment, cancer remains one of the leading causes of death in the world and its survival rate is still low. Therefore, the identification and elimination of risk factors for early-stage prevention is still one of the major challenges in cancer prevention.

According to statistics, more than 14.1 million cancer cases were identified worldwide in 2012, of which 8.2 million died. In addition, almost 300 000 cases of lip and mouth cancer were reported in 2012 with nearly 14 500 deaths. South &Central Asia is one of the regions with the highest incidence.[1] The prevalence of oral cancer in Iran is similar to that of South Asia.[2] In addition to genetic changes, many factors are involved in the development of oral squamous cell carcinoma (OSCC), including age, gender, smoking, alcohol consumption, chemical and physical stimuli, viruses, and hormonal effects. OSCC is 1.91 times more common in men than women, possibly due to higher alcohol and cigarette consumption.[2-7]

Tobacco use is the main risk factor for OSCC.[3-6] Tobacco is mainly used either in smoking forms, such as cigar, cigarette, pipes, or hookah smoking, or in smokeless form like sniffing naswar and chewing tobacco. The diversity of consuming tobacco is high throughout the world due to economic, social, geographical, and cultural conditions as well as a variety of traits in different ethnic groups. For example, naswar is one of the most common types of tobacco used in some parts of southeastern Iran. Smoking, opium use, and poor oral hygiene have been linked to oral cancer in Iran.[8] However, the effects of using cannabis, heroin, and other addictive substances on the development of head and neck squamous cell carcinoma

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(HNSCC) have not yet been confirmed. Many people who use these substances are unaware of their adverse effects and the prevalence of oral cancer is increasing, especially in the lower socioeconomic classes.[9]

All sorts of alcoholic beverages such as wine, beer, liquor, etc. have been found to be associated with oral cancer. With alcohol, the likelihood of developing OSCC depends on the amount and duration of consumption. Alcohol and tobacco consumption have a synergistic effect on the development of OSCC caused by dehydration and increased mucosal permeability. Liu et al. showed that among the risk factors, the consumption of both alcohol and tobacco had a synergistic effect on cancer.[10] Blood type is another risk factor and different cancer incidence rates have been reported in people with different blood types. Possible mechanisms for the association of the blood type and cancer could include immunocompetence inflammation in malignant cell identification, cell adhesion, the presence of ABO antigens in the epidermal growth factor receptor along with other carcinogenic factors such as the binding of ABO antigens involved in carcinogenesis.[11] Diet and body mass index (BMI) also influence carcinogenesis. Other factors, such as occupation, lifestyle, physical and environmental conditions, public perception of physical and mental health, access to health care, dietary and behavioral habits, and oral hygiene are considered risk factors for OSCC. People with poor economic conditions and little education, for example, those who live in deprived areas, may be at higher risk.[12]

By considering the risk factors and precancerous lesions, head and neck cancer as one of the most common cancers can be prevented and prognosis can be improved. Because risk factors vary from region to region, we investigated most of the risk factors for head and neck cancer in patients referred to a specialized oncology center in Mashhad, Iran.

Methods

The present case-control study consisted of 76 patients with HNSCC in the case group referred to Omid hospital at Reza Medical Center in Mashhad, Iran. Patients with HNSCC confirmed by clinical and histopathological examination were included in the study. The control group consisted of 91 healthy individuals who were referred to 5 medical centers in Mashhad, had no history of HNSCC no specific systemic disease and were not taking any particular medication. They were selected using a stratified sampling taking into account their age (over 25 years) and their gender. Subjects and controls were matched according to the age and gender. Those who did not wish to participate in the study were excluded.

Both groups signed a written informed consent prior to the study. The investigator then interviewed all subjects using a structured checklist.[7,13-16] The checklist included questions about demographic information, educational levels, urban or rural setting, family history of cancer, blood types, frequency and duration of tobacco use per day, either in the form of smoking or smokeless (cigarette, hookah, naswar, etc), and duration of tobacco addiction, and alcohol use per day.

Smoking frequency (daily usage) was classified as follows; low ≤ 10, average $10 <$ to ≤ 20, and heavy > 20. The duration of use was also categorized as follows; never: the person had previously smoked less than 100 cigarettes in entire life, before: the person had smoked 30 days before, but not after, and current: the person had smoked more than 100 cigarettes in life and also smoked afterwards.[17] BMI was also calculated by measuring the weight and height using non-digital meters and scales. Periodontitis and oral hygiene were consistently assessed in all patients by examining the rate of attachment loss level (dental pockets) by probing multiple teeth. The frequency of daily teeth brushing and the simplified oral hygiene index (OHI-s) were recorded with scores of 0-2, 2.1-3, and 3.1-6 indicating good, moderate and poor health status, respectively.

The data were collected by field methods and analyzed by descriptive statistics including dispersion and central tendency indices (variance and standard deviation) and statistical charts (pie, histogram). The *t* test was used to compare the means of the two groups with quantitative data, the chi-square test was used to examine the relationship between two qualitative variables, and the Mann-Whitney test was used to compare the means of the rank variables. SPSS 21 software was used for statistical analysis. The significance level was set at 0.05. The odds ratio (OR) of exposure to addictive substances was also determined.

Results

A case-control study of 88 men and 79 women with a mean age of 61.24 ± 11.63 years (25-93 years old in the case and 42-80 years old in the control groups) was performed. The two groups were sex and age matched. A total of 10.5% of the subjects in the case group had a history of cancer and about 3% had HNSCC ($P = 0.002$). The study confirmed significant disparities between urban and rural areas and the majority of the participants in the case group lived in rural areas ($P < 0.001$). There was also a significant difference between the two groups in terms of marital status with a higher incidence of married people in the control group ($P = 0.004$). Table 1 shows patients' demographic and BMI information. The tongue was the most commonly affected area (34.70%).

Table 2 shows that most of the subjects in the control group were addicted to cigarette, alcohol or opium, either alone or in combination ($P < 0.001$, $P = 0.001$, $P = 0.015$). Most of the smokers (66.7%) in the case group were heavy smokers, and the use was significantly higher than in the

Table 1. Characteristics of the study participants

Variables		Case		Control		*P* value
		Number	Percent	Number	Percent	
Gender	Female	32	42.1	47	51.%	0.219
	Male	44	57.9	44	48.4	
Region	Urban	49	64.5	81	89	<0.001
	Rural	27	35.5	10	11	
Education	Illiterate	36	47.4	3	3.3	<0.001
	Less than high school diploma	35	46.1	33	36.2	
	Diploma	2	2.6	39	42.9	
	More than high school diploma	3	3.9	16	17.6	
Age	Mean ± SD	63.09 ± 14.22		59.6 ± 8.71		0.071
BMI	Mean ± SD	23.39 ± 4.34		26.79 ± 4.3		<0.001

*Chi-squared test was used for sex, region and education and independent t test for age and BMI.

Table 2. Frequency and odd ratio of risk factors in the case and control groups

Variables		Cigarette		Hookah		Alcohol		Opium		Naswar	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Case	Yes	21	27.6	6	7.89	7	9.2	24	31.6	9	11.%
	No	55	72.4	72	92.1	69	90.8	52	68.4	67	88.%
Control	Yes	8	8.8	13	14.3	1	1.1	3	3.3	0	0
	No	83	91.%	78	85.7	90	98.%	88	96.%	91	100
P value		0.001		0.314		0.015		<0.001		<0.001	
Odd ratio		3.961		0.609		9.13		13.53		∞	
Confidence interval		(1.639, 9.557)		(0.230, 1.613)		(1.097, 75.963)		(3.886, 47.170)			

Note: Chi-squared test was used for all variables.

control group (Table 3) ($P = 0.016$).

Table 3 also shows that most of the subjects in the control group had never smoked. There was a significant difference between the two groups in terms of the history of cigarette use ($P < 0.001$). As shown in Table 4, the patients used more cigarettes for longer periods of time, and the difference was significant ($P = 0.05$, $P < 0.001$, respectively). In the case of hookah consumption, however, healthy individuals had a longer history of hookah smoking, although the difference was not significant. The duration of hookah consumption in the case group was significantly longer than in the control group ($P = 0.023$). In addition, none of the people in the control group used smokeless tobacco ($P < 0.001$), while 9 people in the case group reported using naswar ($P < 0.001$).

A number of people also cited multiple drug use at the same time, with the majority of the patients using both cigarette and opium (9.20%). Of the 21 cigarette smokers in the case group, 2 (2.62%) smoked only cigarette, while the others consumed it together with other substances. Of the 24 opium addicts, 5 (6.57%) consumed only opium. Naswar was only used in the case group together with other addictive substances (cigarettes or opium). None of the patients in the case group consumed only alcohol, while one person in the control group only consumed alcohol. Reverse smoking was not observed in anyone, and 33.33% of the cigarette smokers kept the smoke in their mouths for a long time, while none of the controls had such a habit, although the difference was not significant ($P = 0.061$). The odd ratio of HNSCC was higher for naswar and opium addicts than for other drugs (∞ and 13.53, respectively). Table 2 shows that the case group smoked more frequently in the past and present than the healthy control individuals.

Among those who were aware of their blood type, the most common blood types in both groups were O + and A +, which were not significantly different ($P = 0.236$). There was a significant difference in BMI between the two groups, and healthy subjects had a higher BMI ($P < 0.001$).

The mean frequency of daily teeth brushing was higher in the control group and the difference was statistically significant ($P < 0.001$). The mean oral hygiene index (OHI) and the mean attachment loss level in the case group were higher than in the control group ($P = 0.306$ and $P = 0.142$, respectively). In addition, the mean pocket depth was higher in the control group; however, the difference was not statistically significant ($P = 0.575$).

Table 3. Frequency of cigarette smoking in the two groups according to the number and status of smoking

	Case		Control		*P* value
	Number	Percent	Number	Percent	
Daily cigarette smoking					
≤10	5	23.8%	3	37.5%	
10>to≤20	2	9.5%	4	50%	0.016
>20/day	14	66.7%	1	12.5%	
Status of smoking					
Current	21	27.6%	8	8.8%	
Former	25	32.9%	10	11%	0
Never	30	39.5%	73	80.2%	

Note: Chi-squared test was used for all variables.

Table 4. Frequency of risk factors in the two groups according to the number and form of addictive substance use

Variables		Duration (year)	Daily cigarette smoking		Kind of habit	
					Number	Percent
Cigarette	Case	6.42±10.58	30.48±9.33	Conventional	21	100%
				Reverse smoking	0	0%
	Control	1.32±3.63	10.25±6.20	Conventional	8	10%0
				Reverse smoking	0	0%
	P value	0.05	<0.001		-	
		Duration (year)	**Daily hookah smoking**		**Manner of using**	
					Number	Percent
Hookah	Case	11.17±6.79	2.5±1.04	Alone	2	33.3%
				Associate	4	66.7%
	Control	5.08±3.88	1.69±0.94	Alone	3	23.1%
				Associate	10	76.9%
	P value	0.023	0.113		0.637	
		Duration (year)	**Daily opium using**		**Manner of using**	
					Number	Percent
Opium	Case	12.63±22.68	2.42±1.47	Smoking	2	87.5%
				Eating	3	12.5%
	Control	9±9.84	1±0	Smoking	2	66.7%
				Eating	1	33.3%
	P value	0.79	<0.001		0.338	
		Duration (year)	**Daily alcohol drinking**		**Manner of using**	
					Number	Percent
Alcohol	Case	3.33±3.5	1.57±0.787	Handmade	2	28.6%
				Industrial	4	57.1%
	Control	3±0	2±0	Handmade	0	0%
				Industrial	1	100%
	P value	0.87	0.629		0.71	
		Duration (year)	**Daily pan using**		**Pattern of using**	
					Number	Percent
Naswar	Case	0.95±3.996	0.34±1.078	Chewing	2	22.23%
				Placing in mouth	7	77.73%
	Control	0	0	Chewing	0	0%
				Placing in mouth	0	0%
	P value	0	0		0	

Note: Chi-squared test was used for qualitative and independent t test for quantitative variables.

Discussion

Most studies have shown that alcohol use and smoking are the main risk factors for HNSCC. Other risk factors such as family history, dietary factors, some viruses, BMI, blood type, and sunlight have also been mentioned in various studies. The aim of this study was to collectively assess the common risk factors for HNSCC in patients who referred to specialized oncology centers in Mashhad, Iran. The use of certain addictive substances, living in rural areas, lower education, lower BMI, and a history of cancer were the main risk factors in the present study, most of which are in line with other studies, including Bakhtiari et al. in southern Iran[18] and Azimi et al in Tehran, Iran.[19]

The main risk factor among addictive substances was for naswar in the case group (OR = ∞), whereas no use of naswar was reported in the control group. Then it was opium with 31.6% and an odd ratio of 13.56. After opium, the highest frequency of cigarette use was with 27.6% and an odd ratio of 3.96. However, these statistics were also applied to subjects who consumed multiple addictive substance. In the present study multiple substances were used in some cases. It appears that the use of multiple substances increases the OR of cancer confirmed in other studies.[20,21]

Higher naswar and opium consumption are related to the geographic and cultural conditions in southeastern part of Iran. Many people who use these products in South Asia belong to the lower socioeconomic classes and are unaware of their negative effects. So, dentists and addiction specialist are responsible for notifying the subjects who use naswar.

Similar studies such as a systematic review reported a higher smoke-free tobacco consumption in the case group and identified the relationship between smokeless tobacco consumption and oral cancer and its OR rate depending on the frequency and duration of use.[22] Khan et al also reported a strong relationship between oral cancer and the Naswar consumption in Pakistan.[23] In Mehdi et al study Naswar was consumed by 15% of SCC patients.[24] Various smoke-free tobacco products appear to play a role in the development of oral cancer due to the increased production of free radicals and DNA damage.[9]

Although opium was the most commonly used addictive substance in both groups, the average daily opium consumption in the case group was significantly different compared to the control group. The high levels of opium consumption in both groups may be due to the fact that opium, along with cigarettes, is the most common drug in the Khorasan Province in Iran, and opium use is not viewed to be as inappropriate or harmful as using other addictive substances in the community, especially by the older people. Other studies also pointed to opium use as a risk factor in Iran.[12]

Hookah consumption has additionally been mentioned as a risk factor in numerous studies. Although there was no significant association between the rate of hookah smoking and the occurrence of OSCC in the present study, the duration of hookah smoking was significantly higher in the case group. Traditional hookah smoking has been common in the past, however, it has become more widespread in recent years, especially among the youth, while most people are unaware of its harmful effects. A review study by Islami et al also confirmed the use of hookahs as a risk factor for OSCC.[25] A systematic review also reported hookah smoking as a risk factor for head and neck cancer with the most common sites being the esophagus, lips, and oral mucosa.[26] Hookah and cigarette contain carcinogens that are toxic to the oral mucosa and the respiratory tract. The nicotine concentration in the blood of people who smoke hookah once a day is equivalent to consuming 10 cigarettes and has harmful effects on the oral mucosa. However, more studies are needed to determine the relationship between hookah consumption and oral cancer.[27]

In the present study, the OR for alcohol consumption was calculated to be 9.133. There was a significant difference between the two groups in terms of alcohol consumption. However, due to the cultural conditions as well as the illegality of alcohol consumption in Iran, many people did not state their drinking or the exact amount of drinking, so the information was not accurate. Various studies have long examined the role of alcohol use as a risk factor for oral cancer. Wang et al. found a strong association between alcohol consumption and OSCC with longer alcohol consumption associated with a higher risk.[14]

Periodontal status was also assessed in this study and it was found that the mean attachment loss level and mean OHI were higher in the case group. Periodontitis as a chronic inflammatory disease increases the proinflammatory cytokines. Periodontal disease has also caused changes in the pathogenic bacteria in the oral environment. These two factors may justify the increased risk of oral cancer in people with periodontitis.[28]

In our study, a family history of cancer was observed in 39.50% of the case group and 37.40% of the control group, although the difference was not statistically significant.

In a case-control study Radoï et al, concluded that the family history must be viewed as a marker for an increased risk of OSCC and that the history of head and neck cancer in first-degree relatives increased 1.9-fold the risk of OSCC,[29] which are not consistent with the results of our study. This may be due to the limited number of participants in our study, as well as differences in the cancer prevalence and the risk factors in different countries.

In this study, the mean BMI in HNSCC patients was significantly lower than in healthy subjects, which may be due to swallowing disorders (dysphagia) and,

consequently, poor nutrition in patients with oral cancer. Radoï et al determined a pre-study BMI in 689 oral cancer patients and 3481 healthy subjects. The results showed an inverse relationship between 5% weight gain over the last two years and cancer.[30]

The most common blood type in patients and healthy subjects in this study was O + , and there was no significant difference between the two groups in this regard. There are only a few studies on the blood type as a risk factor. In a case-control study, Mortazavi et al concluded that most people with oral cancer had type B blood and the OR of OSCC in those with type B blood was 3.5 times higher. The discrepancy may be due to genetic variations.[11]

Conclusion

This study showed that the OR for single use of naswar or opium was higher than that of other addictive substances and that social and cultural conditions play a role in the increased use of these addictive substances. In addition, daily cigarette and hookah smoking, the duration of smoking, and alcohol consumption were significantly higher, and BMI was lower in the HNSCC group than in the control group. Regarding the role of other risk factors, it is advisable to carry out more comprehensive studies with a larger sample sizes in order to achieve more accurate results.

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Competing Interests

The authors declare no conflict of interest in this study.

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