

# Epidemiology of Squamous Cell Carcinoma in Yazd, Iran, from 2001 to 2011

## Original Article

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## Abstract

### Introduction:

Cancer is the second cause of death in the world and the third primary cause in Iran.

In this study, we examined the epidemiology of oral squamous cell carcinoma (OSCC) as the most common malignancy of the oral cavity and its related factors in Yazd Province, Iran, from 2001 to 2011.

### Materials and methods:

This descriptive study evaluated the medical records of patients with OSCC in the chief hospital in the city of Yazd. Data were extracted based on the demographic and primary etiologic, clinical, and pathological characteristics. Data were analyzed with t-test and chi-square test at a significance level of  $\alpha < 0.05$ .

### Results:

OSCC consisted of 54% of the malignancies of the head and neck region, which are most common in the sixth decade of life with a male-to-female ratio of 1.4:1. The average patients' age was 62.81 years. The average annual incidence of OSCC in Yazd indigenous population during the study period was 1.02 out of 100,000 individuals. Overall, 49.3% of patients used tobacco or snuff, and the number of females exposed to these factors was significantly less than that of males ( $P = 0.001$ ). The most common microscopic diagnosis was squamous cell carcinoma (SCC) (76%), followed by verrucous carcinoma (21.1%); 55.8% of patients had well-differentiated SCC, and 42.6% exhibited moderately differentiated SCC. The tongue was the most common site of involvement (41.1%), and the most common clinical feature was exophytic lesions (51.4%).

### Conclusion:

The general epidemiological pattern of OSCC in this study was similar to other studies. In older patients (seventh and eighth decades) and females (particularly in cases of tongue), etiologic factors other than tobacco may play more prominent roles.

**Key words:** •Carcinoma •Squamous Cell •Mouth Neoplasms •Prevalence.

## Introduction

Today, the world is faced with various noncontagious diseases known as modern epidemic.<sup>(1)</sup> Meanwhile, cancer is the second cause of death in developed and developing countries among the 10 most common causes of mortality.<sup>(1)</sup>

Based on studies conducted in Iran, cancer is the third cause of death, and annually, more than 30,000 patients die due to the malignancies. Based on the published data, 55,855 cases of cancer were reported in Iran in 2006.<sup>(2)</sup> Cancer can affect any tissue or organ. Oral cancer is an important issue among health topics.<sup>(3)</sup> Oral cancers include cancers of the lips, tongue, salivary glands, and other intraoral regions and also pharyngeal cancers, including cancers of the nasopharynx, oropharynx, and hypopharynx.<sup>(4)</sup>

Squamous cell carcinoma (SCC) accounts for 90-94% of oral malignancies.<sup>(5)</sup> In this study, SCCs of the lips, tongue, and other intraoral areas with oropharyngeal SCC were collectively evaluated as oral SCC (OSCC). The prevalence of OSCC is different in terms of age, gender, race, and geographic location<sup>(6)</sup>, and approximately 3% of all cancers occur in men, with 2% occurring in women.<sup>(5)</sup> According to data published by the Ministry of Health in Iran in 2003, oral cancers in Sistan and Baluchestan, Chahar Mahal Bakhtiari, and Khorasan Provinces account for 5.9%, 3.4%, and 3.1% of all cancers all over the body, respectively, and are one of the 10 most common cancers.<sup>(7)</sup> OSCC is important due to its disease- or treatment-related complications and high mortality rate.<sup>(5)</sup> Large differences in the annual worldwide incidence and mortality rates of OSCC are found, with variations of up to 20 times between different countries. Most of these differences are undoubtedly due to differences in habits, expectations of life, quality of preventive education, and medical records in different countries.<sup>(6)</sup>

Epidemiological studies (involving patterns of health and illness and associated factors in the population) form the foundation for health-related research and help identify risk factors for disease and render ideal treatment.<sup>(7)</sup> Despite a few studies on Iranian OSCC epidemiology<sup>(8-11)</sup>, there are very limited data available on the exact number of disease-related factors in Yazd; therefore, in the present study, we aimed to

investigate the epidemiology of OSCC from 2001 to 2011 in Yazd as an important city in the center of Iran, with several patients referring from other cities and neighboring provinces.

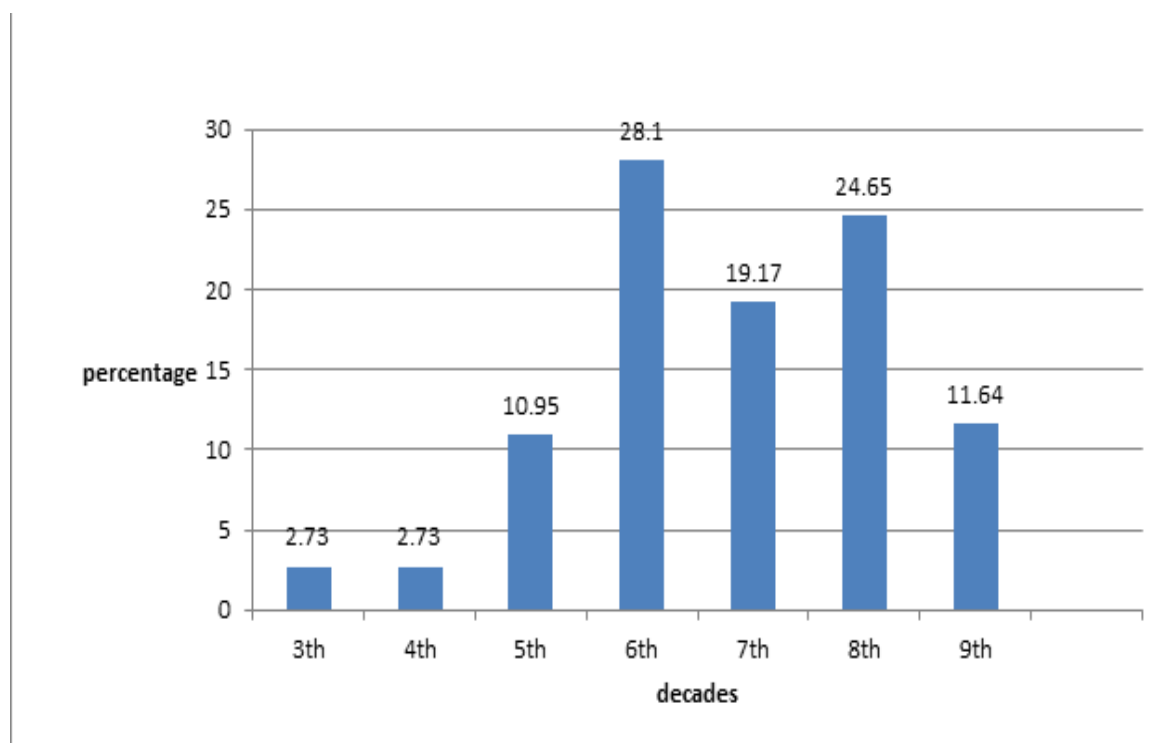
## Materials and Methods

This descriptive cross-sectional study examined the epidemiology of OSCC in a period of 11 years from 2001 to 2011 in Yazd.

Census method was used to evaluate the patients' records in the chief hospital in Yazd during this period, which involved the diagnosis and treatment of patients with OSCC, after the necessary permission. Information required consisted of demographic data (age, gender, whether native or not); possible etiologic factors (smoking and use of smokeless tobacco); and some clinicopathological characteristics (site of the lesion, results of microscopic examinations, and clinical features) of the cases. SPSS version 15 software and descriptive statistical methods were used. Some specific results are presented in tables and graphs. Data were analyzed with t-test and chi-square test at a significance level of  $\alpha < 0.05$ .

## Results

Malignant neoplasms in the population under investigation comprised 11.9% of the head and neck lesions. The relative frequency of OSCC was 54%. Of these patients, 58.2% (n=85) were males and 41.8% (n=61) were females and the male-to-female ratio was 1.4:1. The frequency of the disease after five decades, compared to the previous quarter, showed a significant increase, with a decline in the ninth decade of life again (Figure 1). The highest frequency was seen in the sixth, seventh, and eighth decades of life. Patients aged 50 years and above comprised 83.5%, whereas only 5.47% of patients were 40 years old or younger. The average age of the patients was  $62.81 \pm 15.36$  years, with a mean age of  $63.98 \pm 14.35$  years among men and  $61.96 \pm 16.07$  years among women. The difference between the age groups was not significant according to t-test ( $P=0.435$ ). The average annual incidence of the disease in every 100,000 persons was 1.02, and 75.3% (n=110) of the patients were indigenous people (residents of Yazd, regardless of birth place) and 14.3% (n=21) were not native.



**Figure 1.** Relative frequency percentage of patients according to decades

The status of 10.4% (n=15) of the patients was unknown. Etiologic factors of smoking, snuff, or both were observed in 49.3% of the patients, while 22.6% did not have any of these factors, and the status of 33.56% cases was unknown due to defects in the medical records. The relative frequency of smoking and snuff use specifically decreased with patients' age (Figure 2).

Regarding the relationship between the above risk factors and gender, the chi-square test showed that females had significantly less smoking habit or snuff use, compared with males (P=0.001). Most of the microscopic diagnoses included SCC (76%, n=111), followed by verrucous carcinoma (21.1%, n=31), papillary SCC (2%, n=3), and finally spindle cell carcinoma (0.68%, n=1).

**Table 1.** Grade of OSCC differentiation based on gender

gender	female		male	
	percent	number	percent	number
Well diff	55.8	34	65.9	56
Mod diff	42.6	26	29.4	25
Poorly diff	1.6	1	4.7	4
Total	100	61	100	85

Well-differentiated SCCs comprised the most frequent type of SCCs, with 65.9% in males and 55.8% in females, while poorly differentiated SCCs were least frequent, with 4.7% in males

and 1.6% in females. Accordingly, it was observed that the frequency of well-differentiated grade in males was higher than that in females and the frequency of moderately differentiated grade was higher in females than in males (Table 1). However, these differences were not significant (P=0.124).

The relative frequency of different grades of OSCC was calculated according to age decades (Figure 3). Based on this, except for the third and fourth decades of life and the poorly differentiated grade (due to the low number of patients), with increasing age, the frequency of well-differentiated and moderately differentiated grade increased and decreased in the fifth to eighth decades, respectively. The most common sites of involvement are shown in Figure 4.

Regarding the relative frequency of tumor site and gender, the results showed that the frequency of lesions in the lower lip was slightly lower in men than in women, but this difference was not significant (P=0.373). Tongue lesions were common in both genders, with a higher prevalence in women than in men, although this difference was not significant (P=0.82). The incidence of lesions in the floor of the mouth was significantly higher in men than in women (P=0.023) (Table 2).

Unfortunately, clinical information about the shape and color of lesions was limited or incomplete in most cases.

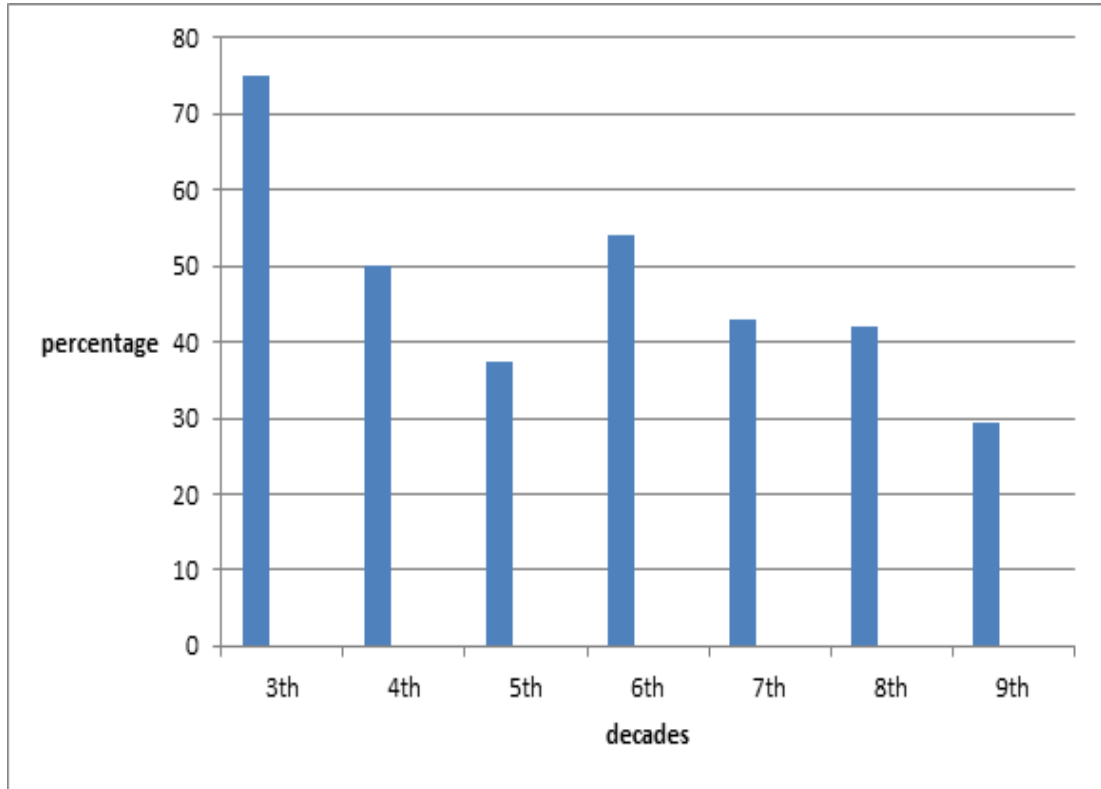


Figure 2. Relative frequency percentage of smoking or snuff according to decades

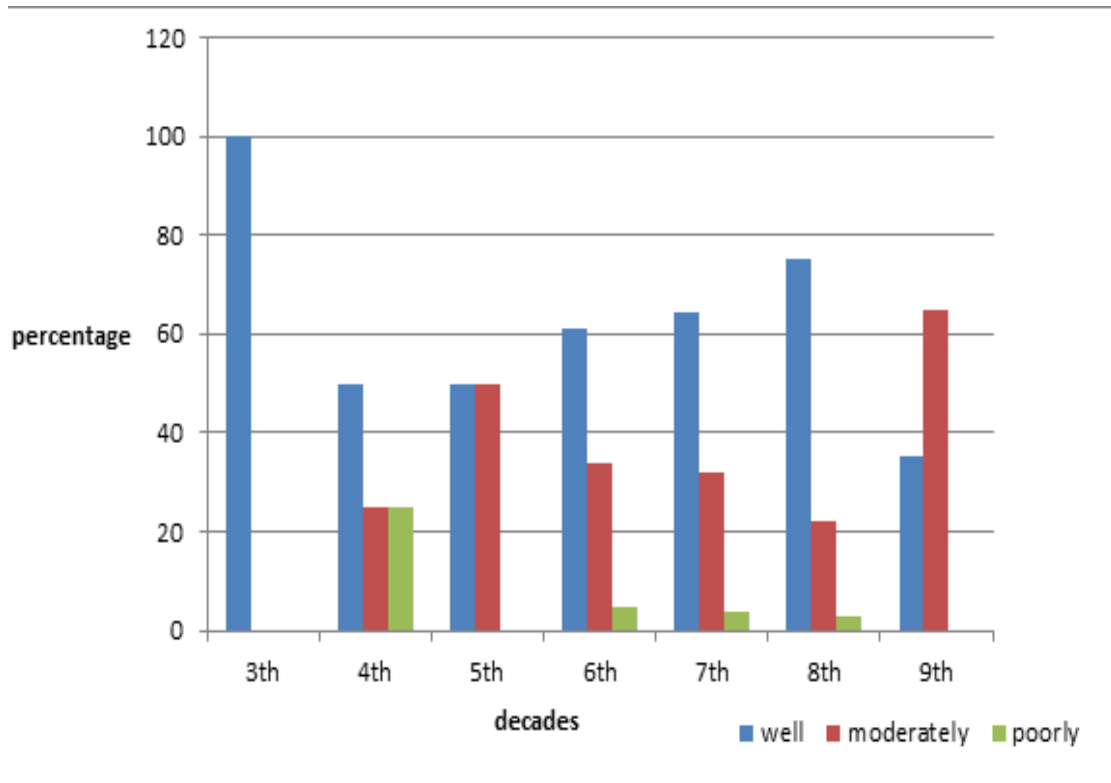


Figure 3. Relative frequency percentage of degrees of differentiation according to decades

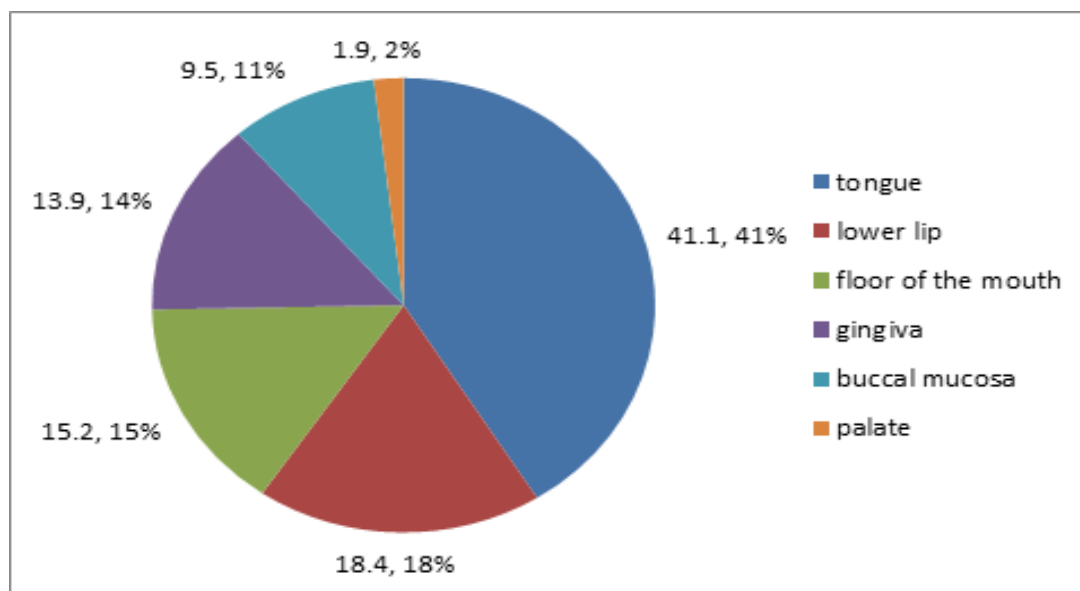


Figure 4. Sites of involvement by OSCC

Table 2. Relative frequency of tumor site based on gender and population

gender					
Location	male	female	Total	Relative frequency of population	P.value
Lower lip	(17.9%)19	(19.2%)10	29	18.4	0.373
Tongue	(27.2%)43	(42.3%)22	65	41.1	0.082
Mouth floor	(17.9%)19	(9.6%)5	24	15.2	0.023
Alveolar mucosa	(11.3%)12	(13.5%)7	19	12	0.640
Buccal mucosa	(7.5%)8	(13.5%)7	15	9.5	0.685
Gingiva	(1.8%)2	(1.9%)1	3	1.9	1
Hard palate	(2.8%)3	0	3	1.9	0.265
Soft palate	0	0	0	0	1

Fishers Exact Test

Regarding the clinical features, lesions with the highest frequency included exophytic lesions (51.4%, n=75), followed by endophytic and ulcerated lesions (15.7%, n=23), and the least frequent form was endophytic lesions (3.4%, n=5). Clinical features were not listed in the hospital records for 29.5% of the cases (n=43).

## Discussion

Based on the above results, OSCC included cancers of the lips, tongue, or other intraoral areas and also oropharynx, constituting 54% of the cancers of the head and neck region. Delavarian et al. reported that 73% of the oral cavity malignancies were SCC in Mashhad in 2009.<sup>(10)</sup> Andisheh Tadbir et al reported that 90% of the oral and maxillofacial malignant tumors were of epithelial origin in Fars Province in 2008.<sup>(11)</sup> Another study by Razavi et al. in Isfahan in 2012<sup>(9)</sup>

reported that 60% of oral cancers were OSCC. Elter reported an incidence rate of 93% in America in 1989<sup>(12)</sup>; Sugerman reported a rate of 98% in Australia in 2002<sup>(13)</sup>, and Arotiba reported a rate of 43% in Nigeria in 2006.<sup>(14)</sup> The differences in these statistics maybe attributed to several factors, including racial differences, absence of registration, or registration with incomplete information, and lack of consideration of lip and oropharynx SCCs as an OSCC. It can also be due to the wider population studied (cancer of the head and neck area).

Because environmental factors are more important than genetic factors in the development of OSCC<sup>(6,16)</sup>, Yazd Province residents, regardless of their birthplace, were considered as indigenous. Based on this, 75.3% of the subjects were native and 21.2% non-native, with 3.5% having an unknown status.



The average annual incidence of cases (new cases per 1,000 people per year) <sup>(6)</sup> among the indigenous population in Yazd Province was 1.02, suggesting a relatively low incidence of oral cancer in this population. In the study by Razavi et al.<sup>(9)</sup>, only 23% of cases were observed during 1991–2000, but 77% of cases were reported during 2001–2010. This observation indicates that the incidence of oral cancers had increased in recent years in Isfahan.

In this investigation, the male-to-female ratio was 1.4:1, which is consistent with those reported by Arotiba in Nigeria <sup>(14)</sup> with a 1.56:1 ratio and by Pires <sup>(17)</sup> with a 2:1 ratio. However, according to some other studies, the male-to-female ratio of OSCC has been reported to be 2 or more.<sup>(3,9,11,15,18)</sup> In contrast, Delavarian et al reported a male-to-female ratio of 0.7:1 in Mashhad Dental School in patients with OSCC from 1999 to 2005.<sup>(10)</sup> Similar incidence rates in female and male populations in recent years might be attributed to changes in habits such as an increase in smoking and consumption of smokeless tobacco among women <sup>(15)</sup> or a decrease in the incidence of SCC of the lip area because of a decrease in men's outdoor activities <sup>(6)</sup> or due to a referral bias because more women than men visit treatment centers as reported by Delavarian et al.<sup>(10)</sup> Age has a significant effect on overall cancer risk <sup>(19)</sup>; most patients with OSCC in the present study were in the sixth, seventh, and eighth decades of their lives (50–79 years) (Figure 1). These results are consistent with those reported by Liewellyn et al.<sup>(19)</sup> and Delavarian et al.<sup>(10)</sup> The present study showed that 83.5% of patients were aged 50 years and above, which is consistent with the results reported by Scully et al. in 2000 in UK <sup>(20)</sup> with 86%, but is in contrast with the observation of Bushra et al.<sup>(21)</sup> in Pakistan in 2011, with a rate of 62%. The differences might be attributed to differences in exposure to potential etiologic factors in different regions of the world and to differences in habits and lifestyles.

The mean age of the patients in the present study was 62.8 years. Chen <sup>(22)</sup>, Delavarian et al.<sup>(10)</sup>, and Razavi et al.<sup>(9)</sup> reported mean ages in their studies to be 52, 53.52, and 52 years, respectively. In the present study, the overall mean age of women (61.96 years) was less than that of men (63.98

years), with no significant differences ( $P=0.435$ ). These results are consistent with those of studies by Delavarian et al <sup>(10)</sup> and Eshghyar et al.<sup>(8)</sup>, but are in contrast with the results reported by Pires et al <sup>(17)</sup> and Arotiba et al.<sup>(14)</sup>

In some studies, the lower average age of women compared to men was justified by the widespread use of smokeless tobacco as a substitute for cigarette in young women <sup>(14,22)</sup>, infection with human papilloma virus (HPV) <sup>(23)</sup>, or chronic iron deficiency anemia in women.<sup>(24)</sup>

In this study, we investigated the possible etiologic factors that have been identified as major general risk factors. A total of 49.3% of patients used smoke, snuff, or both. However, this proportion could be higher because 33.56% of the patient medical records were incomplete and unclear. These results are consistent with those reported by Khandekar et al.<sup>(1)</sup>, Perez et al.<sup>(3)</sup>, and Sharma et al.<sup>(25)</sup>, indicating that the habit of smoking or chewing tobacco was the primary etiologic factor.

This study also showed that the frequency of contact with the abovementioned etiologic factors decreases with aging (Figure 2).

Thus, in general, it can be concluded that although smoking and smokeless tobacco are the important risk factors at any age, with aging from the sixth to ninth decades of life, their role gradually decrease, and probably other unknown factors become prominent. In this regard, factors such as chronic iron deficiency anemia in the elderly <sup>(5)</sup> or nutritional deficiencies, including lack of certain vitamins such as A, C, and E <sup>(6)</sup>, can be mentioned. The present study examined the relationship between possible risk factors and gender, and the results showed that smoking or using snuff in females was significantly ( $P<0.001$ ) less frequent compared with males. The large difference between men and women in terms of exposure to the above factors (16.4% vs. 63.6%) did not coordinate with the small difference in the disease frequency between women and men (41.7% vs. 58.2%); therefore, other etiologic factors may be involved among the female population studied. In this regard, the role of factors such as chronic iron deficiency anemia, infection with HPV, and low consumption of fruits and vegetables among women might be considered. The prevalence of microscopic

diagnosis of OSCC in this study was consistent with the results reported by most studies<sup>(1,5,6,10)</sup>. The prevalence of verrucous carcinoma in the present study (22.2%) was higher than the values reported by some studies, i.e., 1–10%.<sup>(6)</sup> Fujita et al. in their study<sup>(26)</sup> propounded the possible role of HPV in the histopathogenesis of oral cavity carcinomas. However, in this study, due to the incomplete information regarding the consumption of tobacco products in the population studied, this relationship cannot be supported. The role of HPV in oral verrucous carcinomas also requires a separate investigation.<sup>(6)</sup>

Regarding the degree of differentiation of the samples, well-differentiated SCC exhibited the highest frequency (52.4%), followed by moderately differentiated SCC (42.6%) and poorly differentiated SCC (1.6%). The results are consistent with some studies in this respect<sup>(8, 27)</sup> and in contrast with some others that reported that moderately differentiated grade was more frequently observed.<sup>(28)</sup> This study also observed that the prevalence of well-differentiated carcinoma was higher in males than in females (65.9% vs. 55.8%), while the prevalence of moderately differentiated carcinoma was higher in females (42.6% vs. 29.4%) (Table 1).

However, these differences were not significant ( $P=0.124$ ). In patients with poorly differentiated carcinomas, the situation was the reverse. However, due to the small number of subjects in this group, data assessment was worthless. We assume that all the carcinomas in women, compared to carcinomas in men, exhibited lower differentiation. These results are in contradiction with the results reported by Eshghyar et al. However, they also found no significant differences between their results<sup>(8)</sup>. The results showed that in general, the grade of tumor increased in the fifth to eighth decades of life (Figure 3), which are consistent with those reported by Eshghyar et al.<sup>(8)</sup>

Regarding the sites of affliction in the present study, the most common location of OSCC was the tongue (41.1%), followed by the lower lip (18.4%), and in the later stages, the floor of the mouth (15.5%), the oral mucosa and alveoli (13.9%), buccal mucosa (9.5%), and the palate (3.5%). Table 2 shows that similar to several studies<sup>(5,6,17)</sup>, in the present study, the tongue was the most commonly affected area in the mouth

in both genders. However, the relative frequency of tongue SCC was higher in women than in men (42.3% vs. 27.2%), although this difference was not significant ( $P=0.82$ ). Since the primary risk factors, including tobacco and its products, are present in women with a less frequency compared to that in men ( $P<0.001$ ), in general, we can probably assume that etiologic factors other than tobacco, especially in tongue SCC, play an important role in women.

Regarding the clinical features, most of the records were incomplete. Overall, the results in this regard showed that the most frequent lesions were exophytic (51.4%), followed by endophytic and ulcerative lesions (15.7%) and white lesions (3.4%); in 29.5% of the patients, the clinical appearance had not been recorded. These results are consistent with studies by Delavarian et al.<sup>(10)</sup> and Al Rawi<sup>(18)</sup>, who reported higher frequencies for exophytic and ulcerative lesions compared with discoloration. Incomplete patient information and failure to maintain records and data are big problems in academic medical centers, which necessitate training and supervision at all levels, because this information is the primary

## Conclusion

Similar to other areas of Iran, in Yazd Province, SCC was the most common malignancy involving the oral mucosa. In terms of age (83.5% older than 50 years), gender (mostly male), location of lesion (mostly in tongue), clinical features (exophytic lesions more than the others) and microscopic grade (mostly well-differentiated), the results were similar to other studies. The results of the present study showed that about half of patients used tobacco or snuff, and the number of females exposed to these etiologic factors was significantly less than that of males and in old (seventh and eighth decades of life) and female patients (particularly, in relation to tongue lesions), some other etiologic factors probably play a role in OSCC.

## Suggestions

Case-control studies are recommended to investigate the role of other possible etiologic factors such as iron deficiency anemia, chronic HPV infection, and low consumption of fruits and vegetables in OSCC in old subjects (seventh and eighth decades of life) and in females (particularly, in relation to tongue lesions).

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